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STUDIES ON IMMUNOLOGICAL DIAGNOSIS AND THERAPY OF PARAGONIMIASIS

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(6) STUDIES ON IMMUNOLOGICAL DIAGNOSIS
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Contents

Abstract

A. Chemotherapy of Paragonimiasis with Bithionol
III. The follow-up studies for one year after treatment with Bithionol.

The authors reported on the chemotherapy of 13 paragonimiasis patients with Bithionol for the first time in the previous report. In the present study, several examinations of complement-fixation tests, chest X-ray examinations and stool examinations were performed on the above mentioned cases for 1 year after treatment. Strongly positive reactions in complement-fixation tests before treatment became negative within 3 months to 9 months after treatment in all cases.

The abnormal shadows in the chest X-ray found before treatment also disappeared within 1 year after treatment. No ova were found for 1 year after treatment.

The follow-up examinations with complement-fixation tests and chest X-ray examinations after treatment would be the more exacting methods of criterion of cure.

Abstract

B. Epidemiological survey for paragonimiasis in the west district of Shizuoka Prefecture, Japan.

The epidemiologica surveys for paragonimiasis using intradermal tests, complement-fixation tests and stool examinations were conducted in Ōigawa-chō and Ōhama-chō, west district of Shizuoka Prefecture, Japan. Main observations as follows :

1) In Ōigawa-chō, 11 out of 1,023 school children and 5 out of 814 inhabitants showed positive or doubtful reactions in the intradermal tests, but those who showed positive or doubtful skin reactions were all negative in complement-fixation tests and stool examinations. In Ōhama-chō, 28 out of 2,232 school children and 163 out of 4,423 inhabitants were positive or doubtful in intradermal reactions. 66 and 17 out of these 192 positive or doubtful reactors of intradermal test showed positive reactions in complement-fixation tests and paragonimus eggs in stool.

2) Eriocheir japonicus collected in Ōi-river (Ōigawa-chō) were all negative for metacercariae of Paragonimus westermani, but in those which collected in Kiku-river (Ōhama-chō) the metacercariae were detected.

Abstract

C. Chemotherapy of paragonimiasis with Bithionol.
IV. The observations for 6 months after mass-treatment of paragonimiasis patients with Bithionol in Ōhama-chō, Shizuoka Prefecture, Japan.

The non-hospitalized mass-treatment with Bithionol was performed on 16 paragonimiasis patients in Ōhama-chō, Shizuoka prefexture, Japan, and these patients were followed up for 6 months after treatment with serial examinations of intradermal test, complement-fixation test and stool examination.
The main observations were as follows :

1) The same efficacies of treatment as in the hospitalized treatment were found and no relapses nor increase of side effects of drugs could be found.

2) The positive reactions in complement-fixation test of these 16 cases turned negative within 5 months after treatment.

3) In the intradermal test with V.B.S. and ppt antigens, neither disappearance nor tendency of decrease of the diameters of the wheals were found from the follow-up studies for 6 months, and any effects of sensitization of the skin site caused by the repeated injections of these antigens was not found.

4) About 80 γ/cc - 180 γ/cc of Bithionol were kept in blood continually all through the period of treatmen, and disappeared on the 5th day after the completion of the administrations of drug.

Abstract

D. Studies on the complement-fixation test for Paragonimiasis as the method of criterion of cure.

The serial examinations of complement-fixation tests were performed on 48 paragonimiasis patients who have treated with Bithionol or Emetine combined with sulfonamid, and the dilution titers of antiserum taken before, during and after treatment were compared.

The antibody titers in complement-fixation test of the patients who had cured completely showed a tendency of decrease immediately after treatment and finally became negative during the period from 1 month to 12 months after treatment. On the contrary, the antibody titers of the patients who had not cured showed only strong floctuations but negative reactions. It was confirmed that it may be used for the method of criterion of cure from the results of the complement-fixation tests in the early stage after treatment.

A. Chemotherapy of Paragonimiasis with Bithionol

III. The follow-up studies for one year after treatment with Bithionol.

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Introduction

Since paragonimiasis has clinically a very close resembrance with pulmonary tuberculosis and such a serious cases as cerebral Paragonimiasis are not at all rare, much attentions were paid to this disease lately in Japan. However, as the treatment of paragonimiasis, only the combined treatment of Emetine-Sulfonamids (S. Yokogawa et al,1939, 1940) has been taken until recently, the results being not quite satisfactory either in effects or in side-effects, and still more effective drug has been expected.

Recently, the authors (1960) proved that Bithionol was very effective for paragonimiasis : in the first report (M. Yokogawa et al, 1961) showed experimental chemotherapy on the animals infected with paragonimiasis, in the second report (M. Yokogawa et al, 1961) showed the first trial of Bithionol (Bitin, Tanabe Seiyaku Co. Ltd.) for the treatment of 13 cases of human paragonimiasis and the successfull results of this trial.

By this time, the authors have completed the follow-up observations for one year after the treatment and all the cases were proved to be completely cleared. On this report, the authors present the results of those observations.

Objects

As the objects of this experimental therapy, 13 cases of paragonimiasis (male 11, female 2 ranging from 8 to 38 years of age) were selected (Table 1). All these 13 cases live or have lived in those prevalent districts of this disease, Kochi and Ehime prefectures, and they have all eaten cooked Eriocheir japonicus. The supposed lapse of time from the onset of the disease to this treatment varied from 3 months to 10 years. As mentioned before, because of its very close resembrance in clinical symptoms to the pulmonary tuberculosis, there has often been wrong diagnosis by confusion : in 4 cases among those 13 cases with whom the authors treated, the initial diagnosis were mistaken for pulmonary tuberculosis and they were subjected to the chemotherapy with SM, PAS, INAH : and 9 cases were subjected to the therapy of paragonimiasis with the combined methid of Emetine-Sulfonamids. As subjective symptoms, bloody sputa were seen in 8 cases, and as objective ones, abnormal shadows in chest X-Ray were found in all cases. Parenthitically, No. 9 had cerebral Paragonimiasis complicated pulmonal paragonimiasis with spastic palalysis on left arm and leg, blind (both eyes) and disphasia. These 13 cases were all hospitalized and treated with Bithionol.

Method of Therapy

As for the determining of the dose, the consideration of the side-effects and the blood concectration of Bithionol, the authors described in detail in the previous report 2 and therefore omitted in this paper. The daily dose was 2.0 g - 2.5 g for adults and 1.5 g - 2.0 g for children (40 mg/kg - 60 mg/kg). They were given the above daily dose divided into 3 "takes" immediately after meals every other day. And according to the number of doses given (definition : one dose means one "daily dose"), all the cases were divided into 3 groups (I) receiving 5 doses (No. 1) (II) receiving 10 doses (No. 2 - No. 5) and (III) receiving 15 doses (No. 6 - No. 13) ; the efficacy of the treatment was examined in each divided group.

Method of examination

In order to evaluate the efficacy of the treatment and to examine the side-effects, the following tests were given :

1) Stool examination.

For 2 or 3 days before the treatment and every day during the period of the treatment, E.P.D. was calculated by centrifugation technique using AMS III method, and after completion of therapy, stools for 3 consecutive days every month were examined for eggs with the same method.

2) Sputa examination.

The whole daily output of sputa was collected and after examining whether it was bloody or not, it was fully dissolved with 2 % NaOH (3 to 5 times much as sputa) and centrifugated to make egg counts.

3) Clinical examination.

The authors examined various effects of Bithionol on the internal organs and to detect the side-effects as early as possible, the urine, blood, liver function test and the electrocardiogram were applied successively, with constant caution on the patients' subjective symptoms.

4) Complement Fixation Test.

The complement fixation test was conducted with the sera taken periodically before, immediately after, 1 month, 3 months, 6 months and 12 months after completion of the treatment with the technique of the 50 percent end point titration of complement using V.B.S. antigen (X 5,000).

5) X-Ray examination.

Abnormal shadows in Chest X-Ray films (plate and tomography) before the treatment were classified into 4 types as infiltrative shadow, ring shadow, nodular shadow and strand shadow according to their shapes and natures, and their changes were observed continually.

6) Investigation of health condition after the treatment.

The health conditions for a year after the treatment with Bithionol were observed continually and were examined whether there were such sequelae as chronic toxicosis due to the successive medications of Bithionol.

Results

1) The results of stool examination.

The paragonimus eggs in stools of all cases quickly disappeared after the medications from 2 to 5 doses of Bithionol and no relapses were found in any cases from the results of follow-up examinations for 9-12 months after completion the treatment and no significant differences were seen among those groups receiving 5 doses, 10 doses and 15 doses. Besides, the maximum number of eggs per day (E.P.D.) calculated by centrifugation technique using AMS III method was 23,435 as shown in Table 2 and 3.

2) The results of sputa examination. (Table 2)

Before the treatment, in those 10 cases, several times of sputa were observed daily and the maximum number of eggs per day in the whole sputa was 2,431. The eggs in sputa of these 10 cases were disappeared after the medication from 2 to 5 daily doses of Bithionol. But in those 2 cases, No. 11 and No. 12, a few deformed eggs reappeared transiently in the sputa during the course of the treatment. However, no relapses were found from the results of the follow-up investigations during the period from 9 months to 12 months after the completion of the treatment.

3) The results of the clinical examinations.

(i) The results of urine examination.

On all these 13 cases, no abnormal findings were observed in the urine examinations before the treatment, during the treatment and immediatly after the treatment as shown in Table 4.

(ii) The results of blood examination.

No quantitative change were observed among the erythrocyte counts, leukocyte counts and Hemoglobin, as shown in Table 5 and no qualitative or quantitative changes in leukocyte such as the appearance of immature cells, shift to the left or decrease of lymphocyte. Besides remarkable eosinophilia were not found among those 13 cases before the treatment and one case which have recognized eosinophilia before the treatment was put into normal within one month after completion of the treatment as shown in Table 6.

(iii) The results of liver function tests.

The following examinations were conducted as the liver function tests; Takata's reaction, serum cobalt reaction, serum cholinesterase activity, Meulengracht index, serum protein contents, cephalin-cholesterol test and c-reaction protein. And no abnormal findings were found from the results of these examinations as shown in Table 7.

(iv) The results of the electrocardigram.

In those 6 cases of the 15-dose-regimen, the electrocardigram test was conducted immediately after the completion of the treatment, and no abnormal findings were found.

(v) Sbjective symptoms.

Sputa and bloody sputa: Befor the treatment, sputa were found in 10 cases out of 13 cases except 3 cases of children from one to several times per day and in 8 cases out of these 10 cases were seen bloody sputa. Bloody sputa were generally seen at the time of getting up early in the morning. However, bloody sputa were after the medication from 1 to 6 daily doses of Bithionol, and the amount of sputa was also gradually decreased and finally disappeared and neither bloody sputum nor sputum has been found since the completion of the treatment until now.

Side-effects: During the period of the administration of Bithionol, 12 cases out of 13 cases showed such symptoms in digestive organs as diarrhea, loose stools, abdominal pain, nausea or vomiting and 2 cases had urticarial eruption. However, all these side-effects were transient and mild, so scarcely needed either symptomatic treatment or stopping the administration of Bithionol except the 2 cases urticariae eruptions. Besides in the case No. 9, the spastic paralysis on the left limb, blindness, aphasia were not improved even after the administration of the drug. Again, from the results of 2 female cases, menstruation was normal both during and after the treatment and no effect caused by the administration of this drug could be noted. (Table 8)

4) The results of complement fixation test. In 11 cases which could be observed continually, it was proved that some cases showed negative reaction in complement fixation test immediately after the treatment, others showed the decrease of antibody titer gradually after the treatment and finally became negative: in one case immediately after the treatment, in 2 cases 2 months after, in 3 cases 6 months after, in the rest 5 cases, 12 months after the treatment. No particular relations were found between the time of becoming negative in complement fixation test and age, sex, or the number of aggs (E.P.D.) of patients, but in the authors' cases the following relation was noted between the lapse of months before the reaction turned negative and the antibody titers before treatment. That is, those 6 cases which became negative within 6 months after the treatment were all less than X50 in antibody titers before the treatment, while 4 cases out of 5 cases which turned negative in the 12 months after the treatment showed more than X160 in antibody titers as shown table 9 and Fig. 1. Thus the relation between the antibody titers before the treatment and the time of turning negative can be seen to some extent, but this still needs further investigation.

5) The results of X-Ray examination.

The result of Chest X-Ray examinations taken periodically after treatment are shown in Table 10. 5 cases were as early to show curative tendency as immediately after the completion of the treatment.

Besides, in other cases, most of those abnormal X-Ray shadows disappeared between the period from 3 to 6 months after the treatment. In cases where more or less abnormal shadows were noted, those shadows completely disappeared after a year and all the cases were proved to be cured up from X-Ray views.

6) Health condition.

Except the case (No.13) which was complicated with an acuta nephritis caused by an acute tonsillitis in the 9th month after the administration of Bithionol, in other 12 cases the authors could not found any remarkable contraction of a disease at all as shown in Table 11. Besides in 2 female cases, no abnormal menstruation was noted.

Discussion

Bithionol is a tasteless, odorless and white crystalline powder and it was originally used as a skin sterilizer added in soap or cosmetics, but Sawada (1957) found that this agent had an excellent anti- helminthic effect on the chicken tape worm (Railletina kashiwarensis), and later Ueno et al (1959) noticed its same efficacy on the liver fluke of cattles, Fasciola hepatica, and at present this drug is very widely used in general as an anti-helminthic drug for animal use.

Since the authors introduced this drug as therapeutics of paragonimiasis [illegible] can be expected as having a remarkable killing potency, the efficacy has been confirmed by many investigators in Japan. The results summed up by Miyazaki (1961) on 61 cases including the authors' 13 cases read as follows: sputa and eggs in stool disappeared in 1 to 8 times of administration of Bithionol. And it is reported that no case out of all 61 cases has seen recurrence after treatment; 13 cases (the authors' cases) in 6 months after the completion of the treatment; 15 cases, from 3 to 5 months; 27 cases from 1 to 3 months; 6 cases within a month. Komiya, Yokogawa et al (1952) reported that after trial of mass treatment of this disease with the combined method of Emetine-Sulfonamid for consecutive 12 days most of the relapses were seen within 3 months at laters and at least 3 months of follow-up study should be necessary for judging the cure of this disease. It is followed from this fact that out of the above mentioned 6 cases, 28 cases may be assumed their complete cure since no recurrence was found after their treatment. However, this drug is different from Emetine hydrochloride in its function and therefore on the period of follow-up observation in the case of treatment with this drug needs further investigation. But in 13 cases in the authors' present study, there were noted no recurrence in the follow-up studies for one year, which is likely to indicate the complete cure of paragonimiasis by this drug. Besides, in the present cases, no difference in the efficacy of the treatment was noted at all among 5-dose-regimen 10-dose-regimen and 15-dose-regimen; but judging from the disappearance of the eggs and blood concentration, the authors think the most proper administration to be giving 10 doses every other day.

It is again thought to be necessary that the authors examine about the reduction of dose or the duration of the treatment.

As the side-effects caused by the administration of Bithionol, the authors observed in 12 out of 13 cases (except one case which did not show any side effect at all), diarrhea and tendency of loose stool for 9 cases (69.2%), abdominal pain for 5 cases (38.5%), nausea for 3 cases (23.1%), vomiting for 2 cases (15.4%), urticarial eruption for 2 cases (15.4%); but they were all transient and mild, and no case was stopped administration of Bithionol for those sideeffects. In Miyazaki's report, the mentioned 34 cases (excluding the authors' cases), showed diarrhea and tendency of loose stool 13 cases (38.2%), urticarial eruption 6 cases (17.6%), nausea 4 cases (11.7%) and other symptoms as abdominal pain, loss of appetite, headache, and again these are all trasient and mild, and no case was stopped its administration of Bithionol. Besides, the results of the examinations of urine, blood, liver function, electrocardigram done by the authors consecutively till just after the completion of the treatment and the examination of a contraction of a disease for a year after the treatment, are likely to prove there is no danger of chronic toxity caused by the administration of this drug.

Yokogawa (1956, 1961) has often stated the close relation between the complement fixation test in Paragonimiasis and the survival of worms. That is, the intradermal test can't be the standard of assuring the cure of this disease because, once infected with this disease the test keeps positive reaction for such a long period as 10 to 20 years even after the cure of the disease; while the complement fixation test, showing the immediate change by cure, etc., can serve for assuring the cure. Yokogawa (1956) applied this to the patient whose worm cyst in the lung was removed surgically, by conducting the complement fixation test before and after the operation, and proved that the antibody titers in complement fixation test gradually decreased and turned negative after 4 months. Takano (1960) conducted the complement fixation test consecutively for 20 cases who were treated with the combined method of Emetine-Sulfonamids; and found the results as follows. That is, 4 cases turned negative within 3 months out of 7 cases which were assumed complete cure and the other 3 cases also turned negative within 6 months, while 5 cases which were not noted any effect of Emetine at all even during the treatment showed no tendency of decrease of antibody titer in complement fixation test. Kushi et al (1960), too, noted quite similar tendency. Besides in all of the authors' cases, the antibody titers in complement fixation test began to decrease immediately after the treatment; 1 case turned negative juat after the treatment, 2 cases after 2 months, 3 cases after 6 months, and the other 5 cases all turned negative after one year. Besides in the authors' cases, the difference in the antibody titers before treatment can be seen clearly between 6 cases which turned negative within 6 months and 5 cases turned negative in later than 6 months: the formers were under X50, the latters, above X160. And it seemed that generally the lower the antibody titers before

the treatment, the earlier they turned negative. This fact may have some relation with the vitality of the worms before the treatment, but it still somehow needs further investigation. However, it can be said that the complement fixation test give a potent proof not only on the diagnosis but on assuring the cure of paragonimiasis.

Abnormal shadows noted in the chest X-Ray examination before the treatment showed the tendency of disappearance, and reduction immediately after the treatment, and all except strand shadow disappeared after 12 months; but the period of change varied by kinds of the shadows. The tendency comes first in the case of diffused infiltrative shadows, shadows of this kind all disappeared during 1 to 3 months; next in the case of ring shadows, while in the case of nodular shadows and undiffused infiltrative shadows, it took far longer period before the disappearance. It is very interesting that, as mentioned above, in X-Ray shadows of paragonimiasis when the efficacy of treatment was observed, most in 3 months, later in 6, others in a year saw the cure and it seems that it gives an important proof on assuring the cure of paragonimiasis with the above mentioned complement fixation test.

SUMMARY

The authors applied Bithionol to 13 paragonimiasis patients for the first time, and got the following results from one year's follow-up study.

1) Given in the daily dose of 2.0-2.5g (adult) and 1.5-2.5g (child) every other day for 5, 10, and 15 times, all the cases were cleared and no relapses were observed.

2) The side-effects of some transient symptoms in digestive organs and some eruptions but no other abominable side-effects could be noted. Besides no such symptoms as chronic toxicosis as the side-effect of this drug could be observed through the follow-up studies.

3) Complement fixation test and the chest X-Ray examination give potent proof not only on the diagnosis of paragonimiasis but on assuring the cure of pargonimiasis.

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Table 1. Description of 13 cases treated with Bithionol.

Case No.	Name	Age	Sex	Lapse of time from the onset of disease to the treatment	Past history with respect to treatment	
1*	M.S.	36	M	about 4 years	SM	10 grams
					PAS	300 grams
					Emetine	20 ampoullae**
2	K.C.	16	F	2 years 3 months	Emetine	16 ampoullae
3	M.R.	19	M	about 5 years	Emetine	5 ampoullae
4	M.K.	11	M	about 4 years	none	
5*	I.M.	9	M	3 years 4 months	SM	25 grams
					PAS	800 grams
6	H.K.	24	M	about 10 years	none	
7*	Y.M.	21	F	5 years 1 months	SM	60 grams
					PAS	3,000 grams
					Emetine	56 ampoullae
8*	H.K.	17	M	5 years 9 months	SM	52 grams
					PAS	2,800 grams
					Emetine	10 ampoullae
9	T.K.	8	M	2 years 10 months	Emetine	6 ampoullae
10	T.T.	35	M	about 2 years	Emetine	40 ampoullae
11	T.M.	15	M	about 2 years	Emetine	10 ampoullae
					Pararosaniline	22 grams
12	S.T.	12	M	about 2 years	not clear	
13	M.S.	38	M	3 months	Emetine	28 ampoullae

* diagnosed wrongly as lung-t.b. and treated with SM (Streptomycine) and PAS (Para-amino-salycylic acid).

** an ampoule contains 1 cc 4 % Emetine hydrochloride.

Table 2. Results of treatment with Bithionol

Group.	Case No.	Name	Age	Sex	No. Items	Before treatment	Dose (gram) and times (days) of administration of B: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
							(days)																					
I.	1	M.S.	36	M	a.		2.0		2.5		2.5		2.5		2.5													
					b.	(+)		-		(+)																		
					c.	+		+		+		+	-	-	-													
					d.				D			D																
II.	2	K.C.	16	F	a.		2.0		2.0		2.0		2.0		2.0		2.0		2.0		2.0		2.0		2.0			
					b.	(+)	-	+	+				-	-			-											
					c.	+	+	+	+	-	-		+	-			-		-		-		-		-	-		
					d.						V																	
	3	M.R.	19	M	a.		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	D		
					b.	(+)				(+)	(+)			(+)														
					c.	+		+++		+++			+								-		-					
					d.																							
	4	M.K.	11	M	a.		1.5		1.5		2.0		2.0		2.0		2.0		2.0		2.0		2.0		2.0	A		
					b.						D																	
					c.	+	++	++	++	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
					d.								U		U													
	5	I.M.	9	M	a.		1.5		1.5		2.0		2.0		2.0		2.0		2.0		2.0		2.0		2.0			
					b.																							
					c.	+	+		+		+	-	+			-	-	-	-	-			-		-			
					d.				A								D	D										
III.	6	H.K.	24	M	a.		2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2
					b.	(+)	(+)	(+)		+	+		-										-					
					c.	+	+	+		+		-				-		-		-		-	-				-	
					d.				D				D	D														
	7	Y.M.	21	F	a.		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2
					b.	(+)	(+)		+	(+)	(+)	(+)					-	(+)										
					c.	+	+		+	-	-	+		-			-	-				-		-			-	
					d.		A												D				D					
	8	H.K.	17	M	a.		1.5		2.0		2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2
					b.	(+)				+	+															-		
					c.	++	++		+++			++			-		-		-		-	-		-		-		
					d.																				N			
	9	T.K.	8	M	a.		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5	1
					b.																							
					c.	+	++		++		++				-			-				-			-	-		
					d.																							
	10	T.T.	35	M	a.		2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2.
					b.	+	+				(+)				+	+			-				-					
					c.	+		+		+		+		-			-	-	-		-		-		-	-		
					d.				D				D															
	11	T.M.	15	M	a.		2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2.
					b.	+															+*				+*			
					c.	+	+	+	+		-	-	-			-	-		-			-		-		-	-		
					d.																			D					
	12	S.T.	12	M	a.		1.0		1.5		2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2.
					b.	(+)	(+)	(+)			(+)	+	+	-						+*								
					c.	+	+	+			+	+			-	-			-		-			-	-	-		
					d.													N			N							
	13	M.S.	28	M	a.		2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5	2.
					b.	(+)			+	+																		
					c.	+	+		+	-					+		-		-			-		-		-		
					d.									U	U													

Group I. Group of the 5 doses regimen. Group II. Group of the 10 doses regimen. Group III

Remarks : a. : dose of Bithionol (grams)

b. : eggs in sputa

(+):Sputa are bloody and positive for paragonimus eggs.

+ :Sputa are not bloody and positive for paragonimus eggs.

- :Sputa are not bloody and negative for paragonimus eggs.

+*:Sputa are not bloody and positive for deformed paragonimus eggs.

d. : side effects

A :Abdominal pain. D :Diarrhea. N :Nausea. U :Urticarial eruption. V :Vomiti

c. : eggs in st

+ :E.P.D. le

++ :E.P.D. be

+++:E.P.D. ab

- :Negati

1

Table 2. Results of treatment with Bithionol

e	Dose (gram) and times (days) of administration of Bithionol																													After treatment					
-	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	1	2	3	6	9	12"
								(days)																							(months)					
	2.0		2.5		2.5		2.5		2.5																										
		-		(+)																															
		+		+		+	-	-	-																						-	-	-	-	-	-
			D			D																														
	2.0		2.0		2.0		2.0		2.0		2.0		2.0		2.0		2.0		2.0																
	-	+	+				-	-		-		-																							
	+	+	+	-	-		+	-		-		-		-	-		-		-	-										-	-	-	-	-	-
	2.5		2.5		V 2.5		2.5		2.5		2.5		2.5		A 2.5		2.5		D 2.5	D															
				(+)	(+)			(+)																												
		+++		+++			+							-			-														-	-	-	-	-	-
	1.5		1.5		D 2.0		2.0		2.0		2.0		2.0		D 2.0		2.0		D 2.0	A															
	++	++	++	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-											-	-	-	-	-	
							U		U																											
	1.5		1.5		2.0		2.0		2.0		2.0		2.0		2.0		2.0		2.0																
	+		+		+	-	+			-	-	-	-	-			-		-												-	-	-	-	-	-
			A								D	D																								
	2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5						
	(+)	(+)		+	+		-								-																				
	+	+		+		-				-		-		-	-	-					-		-		-		-		-	-	-	-	-	-	
			D				D	D																			V		A		D					
	2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5						
	(+)		+	(+)	(+)	(+)					-	(+)																							
	+		+	-	-	+		-			-	-				-		-					-		-	-		-			-		-		
	A																																		
	1.5		2.0		2.0		2.5		2.5		2.5		D 2.5		2.5		D 2.5		2.5		2.5		2.5		2.5		2.5		2.5						
	++		+++		++				-		-		-		-		-		-		-		-		-		-		-	-	-	-	-	-	
																			N																
	1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5		1.5						
	++		++		++				-			-			-				-	-			-		-		-		-	-	-	-	-	-	
	2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5						
	+				(+)				+	+			-				-		-																
		+		+		+	-			-	-	-										-	-		-				-	-	-	-	-	-	-
			D				D										D	D				D	D		D										
	2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5						
	+	+	+		-	-	-			-	-		-			-	-			+*			-		-						-	-	-	-	-	
																			D							D	D								
	1.0	1.5	2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5						
	(+)	(+)		(+)		+		-						+*																					
	+	+		+	+				-	-			-					-	-		-		-		-	-	-			-	-	-	-	-	
											N				N																					
	2.0		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5		2.5						
	+		+	+					+		-		-			-		-		-			-			-			-	-	-	-	-	-	-
								U	U																				D							

doses regimen. Group II. Group of the 10 doses regimen. Group III. Group of the 15 doses regimen.

lthionol (grams)

puta

bloody and positive for paragonimus eggs.

not bloody and positive for paragonimus eggs.

not bloody and negative for paragonimus eggs.

not bloody and positive for deformed paragonimus eggs.

ts

pain. D :Diarrhea. N :Nausea. U :Urticarial eruption. V :Vomiting.

c. : eggs in stool

\+ :E.P.D. less than 3,000

++ :E.P.D. between 3,000 and 10,000

+++:E.P.D. above 10,000

\- :Negative of paragonimus eggs.

Table 3. Variations in E.P.D. in stools and the clearance after the administration of Bithionol. (Sedimentation techniques with the A.M.S. III Method and Stoll's egg counting technique).

Days	Cumulative number of the doses	*	**				***							
		No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12	No. 13
Before	0	122	572			456								
1	1		1,410		4,788	248	258	135	6,860	3,150		350	3,215	1,210
2		656	222	23,435	3,780		738				2,178	84	2,548	
3	2		80		4,224	978		1,625	18,330	7,503		261		1,885
4		1,110	0	8,400	2,494		116	0			1,525			0
5	3		0		792	258		0		6,525		0	639	
6		232			0	0	0	312	4,260		129	0	98	
7	4	0	115	550	0	312						0		
8		0	0		0			0			0			
9	5	0			0				0	0			0	392
10			0		0	0	0					0	0	

* --- Sub-group of the 5-dose-regimen
** --- Sub-group of the 10-dose-regimen
*** --- Sub-group of the 15-dose-regimen

Table 4. Results of Urine examinations

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13
Before treatment													
Glucose	-	-	-	-	-	-	-	-	-	-	-	-	-
Protein	-	-	-	-	-	-	-	-	-	-	-	-	-
Urobilin	-	-	-	-	-	-	-	-	-	-	-	-	-
Urobilinogen	N	N	S	N	N	N	N	S	N	N	N	N	N
Bilirubin	-	-	-	-	-	-	-	-	-	-	-	-	-
Urine sediment	(not remarkable)												
During treatment													
Glucose	-	-	-	-	-	-	-	-	-	-	-	-	-
Protein	-	-	-	-	-	-	-	-	-	-	-	-	-
Urobilin	-	-	-	-	-	-	-	-	-	-	-	-	-
Urobilinogen	S	N	N	N	S	N	N	N	N	N	N	S	N
Bilirubin	-	-	-	-	-	-	-	-	-	-	-	-	-
Urine sediment	(not remarkable)												
After treatment													
Glucose	-	-	-	-	-	-	-	-	-	-	-	-	-
Protein	-	-	-	-	-	-	-	-	-	-	-	-	-
Urobilin	-	-	-	-	-	-	-	-	-	-	-	-	-
Urobilinogen	N	N	N	N	N	N	N	N	N	S	N	N	N
Bilirubin	-	-	-	-	-	-	-	-	-	-	-	-	-
Urine sediment	(not remarkable)												

Remarks : N:normal
S:increased slightly

Table 5. Variations of Erythrocyte counts and Hemoglobin before and after treatment

Case No.	Name	Age	Sex	Erythrocyte counts (X10,000) Before	After	Hemoglobin (%) Before	After
1	M.S.	36	M	448	461	90	90
2	K.C.	16	F	515	495	100	100
3	M.R.	19	M	421	430	90	90
4	M.K.	11	M	429	452	80	85
5	I.M.	9	M	474	442	92	90
6	H.K.	24	M	452	476	95	97
7	Y.M.	21	F	413	405	85	90
8	H.K.	17	M	436	448	89	93
9	T.K.	8	M	490	508	95	95
10	T.T.	35	M	440	464	95	95
11	T.M.	15	M	514	500	100	100
12	S.T.	12	M	522	516	94	95
13	M.S.	38	M	434	409	100	96

Table 6. Variations of Leucocyte count and Differential count before and after treatment.

Case No.	Name	Age	Sex		Leucocyte count	Differential count B.	E.	N 1	2	3	4	5	L.	M.
1	M.S.	36	M	before	7,400	0	6	3	12	21	18	2	34	4
				after	7,700	0	2	4	19	26	15	4	28	2
2	K.C.	16	F	before	7,600	0	2	1	23	28	10	4	16	6
				after	7,000	0	3	2	24	32	6	8	21	4
3	M.R.	19	M	before	7,400	0	12	2	11	19	11	5	38	2
				after	6,900	0	6	4	13	24	9	8	33	3
4	M.K.	11	M	before	8,000	0	6	2	12	32	6	3	31	8
				after	7,400	0	4	2	16	36	9	2	26	5
5	I.M.	9	M	before	6,800	0	1	2	24	29	10	3	27	4
				after	7,300	0	1	4	18	33	5	1	30	8
6	H.K.	24	M	before	7,000	0	6	1	12	18	8	6	41	8
				after	6,400	0	3	2	8	16	7	8	50	6
7	Y.M.	21	F	before	6,900	0	8	2	18	33	5	1	29	4
				after	7,000	0	3	0	16	40	4	3	25	9
8	H.K.	17	M	before	7,200	0	6	4	13	37	6	2	29	3
				after	6,800	0	4	1	8	33	12	4	34	4
9	T.K.	8	M	before	7,400	0	1	3	17	41	14	2	19	3
				after	7,000	0	1	2	20	36	10	4	26	1
10	T.T.	35	M	before	7,300	0	1	2	18	21	7	2	43	6
				after	7,100	0	0	1	17	29	2	3	40	9
11	T.M.	15	M	before	7,000	0	1	2	19	39	5	4	25	5
				after	6,800	0	1	3	24	28	7	3	31	3
12	S.T.	12	M	before	5,600	0	7	1	13	34	8	4	25	8
				after	6,300	0	6	3	21	26	4	6	27	7
13	M.S.	38	M	before	7,100	0	2	2	18	29	8	5	30	6
				after	6,400	0	3	0	16	30	14	3	25	9

Table 7. Results of Liver functions

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13
(Before treatment)													
Takata's reaction	–	–	–	–	–	–	–	–	–	–	–	–	–
Serum cobalt reaction	R5(2)	R4(2)	R5(1)	R3(2)	R4(2)	R4(2)	R4(2)	R5(2)	R3(2)	R4(1)	R3(2)	R4(2)	R4(2)
Serum cholinesterase activity (%)	70–80	80–90	80–90	70–80	80–90	70–80	70–80	80–90	70–80	80–90	80–90	70–80	80–90
Meurengracht index	3	4	5	3	4	4	3	3	4	5	4	4	4
Serum protein (g%)	8.3	8.9	7.6	6.8	7.6	8.0	6.5	7.8	8.6	9.4	8.0	7.8	7.6
Cephalin-cholesterol test	–	–	–	–	–	–	–	–	–	–	–	–	–
c-reaction protein	–	–	–	–	–	–	–	–	–	–	–	–	–
(After treatment)													
Takata's reaction		–		–	–	–					–		–
Serum cobalt reaction		R4(2)		R4(2)	R3(2)	R4(1)					R3(1)		R4(1)
Serum cholinesterase activity (%)		80–90		80–90	70–80	80–90					80–90		80–90
Meurengracht index		4		4	4	4					3		4
Serum protein (g%)		8.4		7.2	8.0	8.2					8.2		8.0
Cephalin-cholesterol test		–		–	–	–					–		–
c-reaction protein		–		–	–	–					–		–

Table 8 Changes of Subjective symptoms

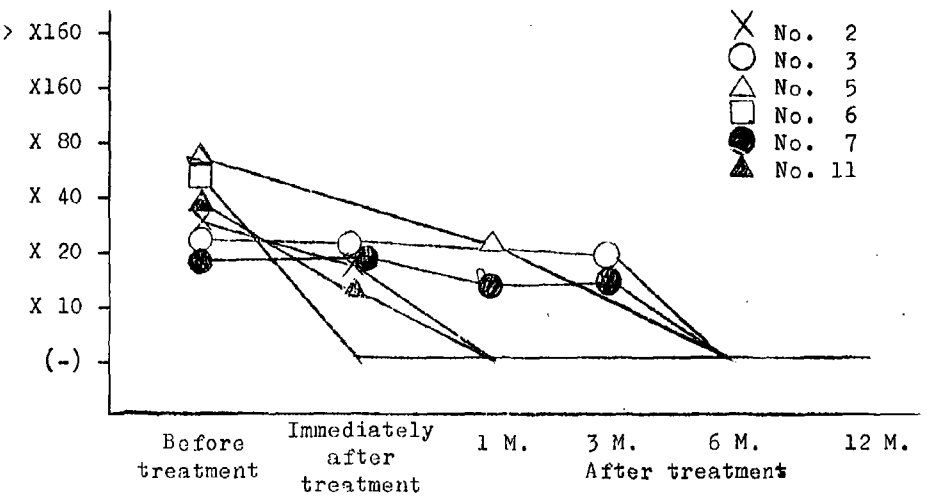
Case No.	Bloody sputa	Abdominal pain	Diarrhea and tendency of loose passage	Nausea	Vomiting	Urticarial eruption	Abnormal menstration	Paralysis of extremity	Disturbance of vision	Disphasia
Before treatment										
1	+									
2	+									
3	+									
4										
5										
6	+									
7	+									
8	+									
9								+	+	+
10			+							
11										
12	+									
13	+									
During treatment										
1			+							
2		+	+		+					
3		+	+							
4						+				
5		+								
6		+	+		+					
7		+	+							
8			+	+						
9								+	+	+
10			+							
11			+							
12				+						
13			+			+				
After treatment										
1										
2										
3										
4										
5										
6										
7										
8										
9								+	+	+
10			+							
11										
12										
13										

Table 9. Changes of dilution titer of Antiserum in Complement-fixation test on the individuals before and after treatment.

Case No.	Age	Sex	Before treatment	Immediately after treatment	After treatment 1 M.	3 M.	6 M.	12 M.
1	36	M	X 68.1	X 40.5			X 27.5	-
2	16	F	X 29.0	X 12.0	-	-	-	
3	19	M	X 25.0	X 23.1		X 20.4	-	-
5	9	M	X 46.5		X 21.5		-	-
6	24	M	X 40.0	-	-		-	-
7	21	F	X 22.4	X 20.0	X 15.1	X 18.6	-	-
8	17	M	> X160.0	X 53.0			X 24.2	-
9	8	M	> X160.0	X 53.3	X 32.3		X 18.8	-
10	35	M	> X160.0	X 86.5		X 55.1	X 18.2	-
11	15	M	X 31.4	X 12.1	-		-	
13	38	M	> X160.0	> X160.0		X 44.6		-

Fig. 1. Changes of dilution titer of Antiserum in Complement-fixation test on the individuals before and after treatment.

(A) 6 cases which became negative within 6 months after treatment.



(B) 5 cases which became negative in 12 months after treatment.

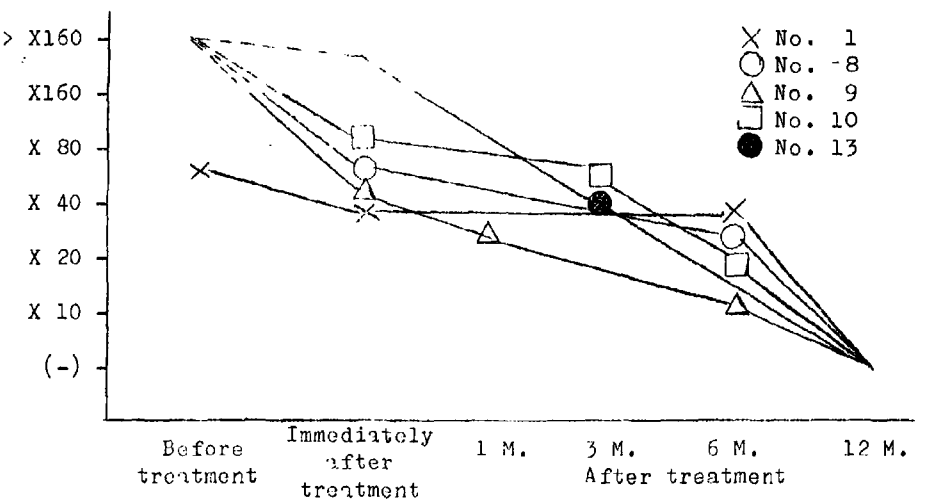


Table 10. The follow-up studies on the chest X-ray findings of the patients treated with Bithionol for 1 year.

Case No.	Age	Sex	Before treatment	After treatment 1-3 days	1 Month	3 Months	6 Months	12 Months	Efficacy
1	36	M	undiffused infiltrative shadow	declined slightly				disappeared	(healed)
3	19	M	nodular shadow	unchanged		redused	redused	disappeared	
			ring shadow	unchanged		unchanged	disappeared		(healed)
			diffused infiltrative shadow	unchanged		declined	disappeared		
4	11	M	nodular shadow	unchanged			strand shadow		
			ring shadow	unchanged			redused		(healed)
			diffused infiltrative shadow	declined slightly			disappeared		
5	9	M	diffused infiltrative shadow	unchanged	disappeared				(healed)
6	24	M	ring shadow	redused		disappeared			
			undiffused infiltrative shadow	declined		disappeared			(healed)
7	21	F	nodular shadow	unchanged		disappeared			
			diffused infiltrative shadow	disappeared					(healed)
8	17	M	nodular shadow	unchanged			disappeared		
			undiffused infiltrative shadow	unchanged			disappeared		(healed)
9	8	M	strand shadow	unchanged	unchanged			unchanged	(healed)
10	35	M	nodular shadow	strand shadow		disappeared			
			ring shadow	strand shadow		disappeared			
			diffused infiltrative shadow	disappeared					(healed)
11	15	M	undiffused infiltrative shadow	unchanged	unchanged	declined			(healed)
13	38	M	slight bronchiactatic shadow	unchanged	declined slightly			disappeared	
			increase of peribronchial marking	unchanged	disappeared				(healed)

Table 11. Health conditions after treatment

Months	Case No. / Sex	1 M	2 F	3 M	4 M	5 M	6 M	7 F	8 M	9 M	10 M	11 M	12 M	13 M
1		-	-	-	-	-	-	-	-	-	-	-	-	-
2		-	-	-	-	-	-	-	-	-	-	-	-	-
3		-	-	-	-	-	-	-	-	-	-	-	-	-
4		-	cold	-	-	cold	-	-	-	-	cold	-	-	-
5		cold	-	cold	-	-	-	-	-	-	-	-	-	-
6		-	cold	-	cold	-	-	-	-	cold	-	-	-	cold
7		-	-	-	-	-	-	-	-	-	-	-	-	-
8		-	-	-	-	-	-	-	-	-	-	-	-	-
9		-	-	-	-	-	-	-	-	-	-	-	-	tonsil-litis acuta
10		-	-	-	-	-	-	-	-	-	-	-	-	nephritis acuta
11		-	-	-	-	-	-	-	-	-	-	-	-	cured
12		-	-	-	-	-	-	-	-	-	-	-	-	-

B. Epidemiological Survey for Paragonimiasis in the West District of Shizuoka Prefecture, Japan.

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Introduction

Epidemiological surveys for paragonimiasis have been conducted in different areas of Japan by many investigators with the mass examination method using intradermal test, since Yokogawa et al (1955) settled this method of mass examination. These surveys made geographical distribution of this disease clear: it is widely distributed in every prefecture except Hokkaido and Aomori, and the number of the infected is presumably not less than a million in the whole country.

In Shizuoka prefecture, the eastern part of it had long before been noted as the endemic area of paragonimiasis, especially the Kano-gawa valley (Yokogawa et al, 1956) and the Aono-gawa valley (Suzuki, 1958) have been reported to be donsely infected. The western part of it, however, has never been investigated and thereby the actual state of the paragonimiasis distribution has been utterly unknown. The authors have resently conducted mass examinations for both school children and inhabitants in Oigawa-cho and Ohama-cho, in the western part of the prefecture, and present the results of them in this paper.

Objects

The present investigation was conducted twice in the districts shown in Fig. 1, Oigawa-cho situated on the mouth of the Oi-river and Ohama-cho on the mouth of the Kiku-river. Namely, the first one was conducted in January, 1961, in Oigawa-cho for 1,842 in total, 1,028 of school children and 814 of general inhabitants; and in Ohama-cho for 2,689 in total, 2,232 of school children and 457 of general inhabitants. The second one was conducted in May 1961 for 3,966 of general inhabitants of the whole Ohama-cho, according to the results of the above first investigation that in this district there were many who were positive for paragonimus eggs.

In addition the mass treatment with Bitin was applied to those in Ohama-cho who showed positive, paragonimus eggs in sputa or stools, the result of which will be reported on another opportunity.

Method

1) Intradermal Test

In every above mentioned investigation district, school children and the general inhabitants were asked to gather at the place of examination by health center and the town office, and intradermal test was carried out according to the method of Yokogawa et al (1955), using 1: 10,000 dilution of Veronal Buffered Saline extract (V.B.S. antigen) prepared from adults of Paragonimus westermani. That is, all individuals were injected intradermally on the volar surface of the left forearm with antigens (0.01cc-0.02cc), the amount sufficient to raise the 3-4mm of the diameter of the wheal. The length and width of the ensuing wheals

were respectively measured in mm. immediately and 15 minutes after the injection. The average values in mm (less than 1 mm was cut down) of the length and width were calculated respectively. The difference between the average value of the wheal raised immediately after injection and that of the wheal raised 15 minutes after is referred to as the increase of the diameter. And the difference of 5mm or more, 4mm, and 3mm or less were condidered as positive, doubtful and negative reactions respectively.

2) Complement Fixation Test.

The sera were taken from all those who showed positive or doubtful reactions to intradermal test and the complement fixation test was conducted using 1:5,000 V.B.S. antigen employing the method of 50 percent hemolysis end point titration described by Yokogawa et al (1956), and more than 1:10 and less than that in dilution of the anti serum were considered as positive and negative reactions respectively.

3) Stool examination.

All those who showed positive or doubtful reaction to intradermal test were asked to bring their stools 3 times intermittently. 0.5-1.0g of stool every day was centrifuged with AMS III method and the whole sediment was examined under the microscope.

4) Examination of the second intermediate host.

Eriocheir japonicus colected in the Oi-gawa and the Kiku-gawa was examined for metacercariae of P. westermani.

Results

The summarized results of the present investigation in Oigawa-cho and Ohama-cho are shown in Table 1. And the two investigations in Ohama-cho separately performed will be reported in colligation for convenience sake.

1) The results of intradermal test.

In Oigawa-cho, among 1,028 school children, positive reactions were 6(0.6%), doubtful reactions 5(0.5%), among 814 inhabitants, positive reactions 4(0.5%), doubtful reaction 1(0.1%): in total, 1,842, positive reactions were 10 (0.5%), doubtful reactions 6(0.3%), so the rate of positive reactions was low both among school children and general inhabitants. While in Ohama-cho, among 2,232 school children, positive reactions were 16(0,7%), doubtful reactions 12(0.5%), and among 4,423 inhabitants, positive reactions were 142(3.2%), doubtful reactions 21 (0.5%): in total 6,655, positive reactions were 158(2.4%) doubtful reactions 33(0.5%). So the rate of positive reactions was as low among school children as in Oigawa-cho but the rate among general inhabitants was found comparatively high.

2) The results of complement fixation test.

Complement fixation test was conducted for all those who were positive or doubtful for intradermal test: in Oigawa-cho, it was conducted for 11 school children and 5 inhabitants, 16 in total; and they were all negative. While in Ohama-cho, positive reactions for this test were

seen in 6(21.4%) out of 28 school children and 60(36.8%) out of 163 general inhabitants: 66(34.6%) out of 191 in total. Being observed from the respects of individuals who showed positive and doubtful reactions to intradermal test in Ohama-cho, all those 6 school children who gave positive reactions in complement fixation test were also positive for intradermal test, and as for general inhabitants 59(41.5%) out of 142 who were positive to intradermal tests and 7(33.3%) out of 21 who were doubtful, gave positive reactions in complement fixation test.

3) The results of stool examination.

Egg examination was conducted, as in complement fixation test, for stools of all individuals who were positive or doubtful for intradermal test. The result was that in Oigawa-cho not one of 16 school children and inhabitants was positive for eggs, while in Ohama-cho 4(14.3%) out of 28 school children and 13(8.0%) out of 163 general inhabitants that is, 17(8.9%) out of 191 in total were found positive for eggs. This makes 0.2% to 2,232 school children and 0.3% to 4,423 general inhabitants, 0.3% to the total objects of the examination in Ohama-cho.

Besides, 17 individuals who were positive for eggs gave positive reactions to both intradermal test and complement fixation test; accordingly eggs were detected in 4(66.7%) out of 6 school children and 13 (21.7%) out of 60 inhabitants who were positive for both tests in Ohama-cho.

4) The result of the examination of Eriocheir japonicus.

As shown in Table 2, no metacercariae was found in 8 Eriocheir japonicus collected in the Oigawa, but in 4(28.6%) out of 14 of the Kiku-gawa, metacercariae of P. westermani were found.

Discussion

The authors confirmed on the basis of the present investigation that paragonimiasis was prevalent in Ohama-cho, along Kiku-river.

A few observations will be added on the results of this investigation in the following.

The percentage of positive reactions in intradermal test.

The percentages of positive reactions in the present intradermal tests both in Oigawa-cho and Ohama-cho, were 0.5% in the former and 2.4% in the latter. This percentage in Ohama-cho was a little low, compared with such average percentages in the eastern part of the prefecture as 3.8% in Kannami-mura, Tagata-gun (et al 1956), 5.9% in South Izu district (Suzuki, 1958). However, as shown in Table 3 and Fig. 2, the percentage of positive reactions in intradermal test in Ohama-cho for general inhabitants excluding school children, observed from the standpoint of each sections, shows high as 14.5%, 8.7%, 7.6%, 6.6%, respectively in Kunikane, Kaito, Kuniyasu and Kikuhama along the Besides 15(88.2%) out

of 17 egg positive individuals (including school children) were found from those 3 sections of Kunikane (8), Kuniyasu (6) and Kikuhama (1), while only 2 (1 from Nakagahara and 1 from Hamano) were found from those sections away from the Kiku-river. The reason of this may be that in those valley districts there were much more opportunities of eating Eriocheir japonicus than in other districts; in fact, the metacercariae of P. westermani were found in Eriocheir japonicus collected in the Kiku-river.

The relation between the titer of antiserum in complement fixation test and the egg positive Percentage.

In the present investigation, 17 egg positive cases found in Ohama-cho were all positive both for intradermal test and complement fixation test. Then 59 individuals who were positive for both test were classified into 5 groups according to the dilution titer of antiserum as shown in Table 4 and Fig. 3. Namely, in the group of more than 1:160 in dilution of antiserum, 12 out of 18, in the group from 1:40 to 1:159 in dilution of antisum 3 out of 9 and in the grup from 1:10 to 1:39 in dilution of antiserum 2 out of 39 were found positive for eggs, accordingly the ratio of egg positive were 66.7%, 33,3%, and 5,1% respectively. However, no eggs were found in the group which was negative in complement fixation.

As Yokogawa et al have often stated, complement fixation test for paragonimiasis, different from intradermal test, would turn negative within several months after the complete recovery of this disease. Therefore intradermal test is very fit for screening the infection of paragonimiasis, regardless of present and past disease, while complement fixation test is an effective method of examining the existence of the present disease; so it seems necessary that, when complement fixation test shows strongly positive, showing a strong probability of the paragonimiasis infection, repeated egg examinations should be conducted.

The authors have observed mainly on the results of the investigation in Ohama-cho where egg positive individuals were found, and the fact attracting special attention in this investigation is that 9 (52.9%) out of 17 egg positive individuals were confused with pulmonary tuberculosis cases: 2 out of 9 cases had been diagnosed and treated as having pulmonary tuberculosis and later on found to be paragonimiasis, and the rest 7 have been treated as pulmonary tuberculosis for 6 months to 2 years up to the present. Such cases can be found every-where and the confusion of these two diseases is important rpoblem in the endemic areas of paragonimiasis. But there is no method to settle the diagnosis of the disease other than stool or sputa examination finding out the Paragonimus eggs; and such immunological diagnosis as intradermal test and complement fixation test and the X-Ray diagnosis are, after all, supplementary methods of diagnosis. However, by using and making the characteristics of the these various methods of diagnosis, comparatively sure diagnosis

can be made. However, there may be a complicated infection with pulmonary tuberculosis, so the diagnosis of paragonimiasis requires circumspection.

In addition, judging from the state in Ohama-cho prevalent of paragonimiasis, the authors surmise that there may be a large number of infected individuals among surrounding towns and villages and hope to take up another oppertunity to conduct further investigations.

Summary

Twice in January and May 1961, the authors investigated the paragonimiasis distribution in Oigawa-cho and Ohama-cho, Shizuoka prefecture. The results are:

1) In Ōigawa-cho, 11 out of 1,028 school children and 5 out of 814 inhabitants showed positive or doubtful reactions in the intradermal tests, but those who showed positive or doubtful skin reactions were all negative in complement fixation test and stool examinations. In Ohama-cho, 28 out of 2,232 school children and 163 out of 4,423 inhabitants were positive or doubtful in intradermal reactions. 66 and 17 out of these 191 positive or doubtful reactors of intradermal test showed positive reactions in complement fixation tests and paragonimus eggs in stools.

2) Eriocheir japonicus collected in Ōi-river (Ōigawa-cho) were all negative for metacercariae of Paragonimus westermani, but in those which collected in Kiku-river (Ōhama-cho) the metacercariae were detected.

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Fig. 1. Localities surveyed in Shizuoka prefecture

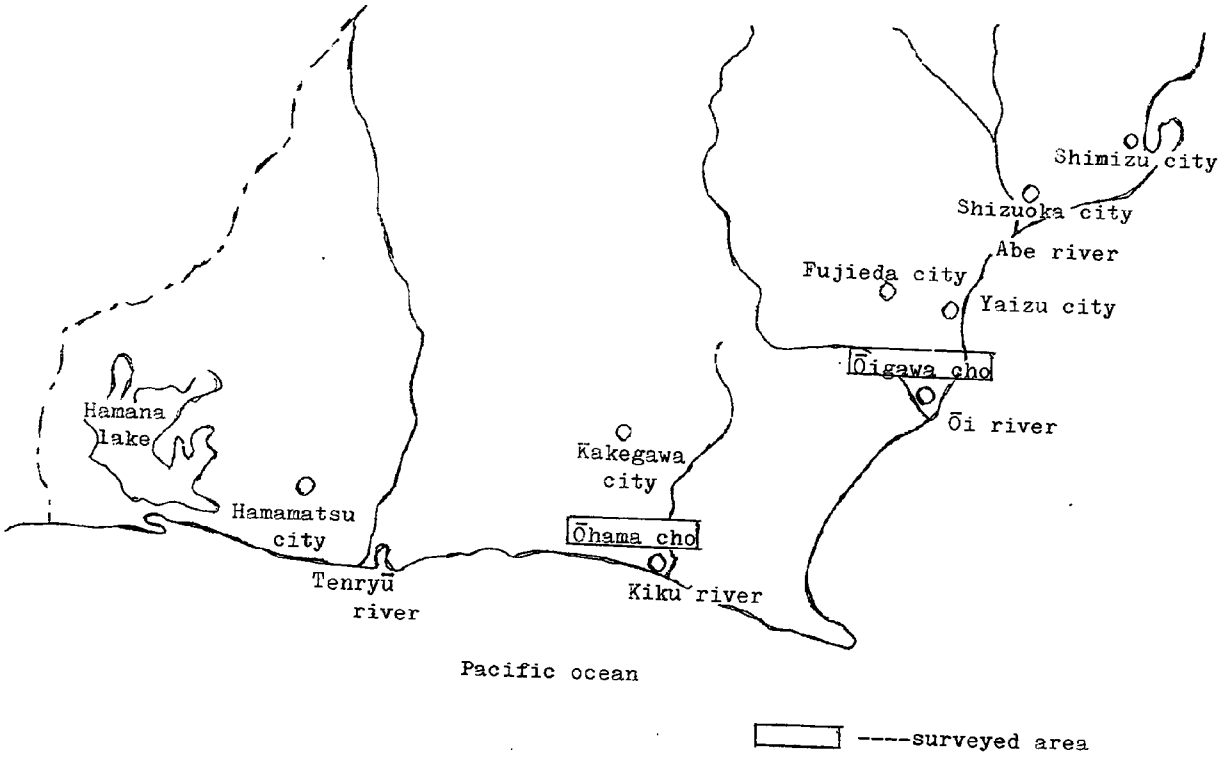


Table 1. Results of Intradermal test, Complement-fixation test and Stool examination.

Location	Objects	No.examined	Intradermal test (+)	Intradermal test (±)	Total	C.F.test (+)	Eggs (+)
Ōigawa-chō	school children	1,028	6 (0.6%)	5 (0.5%)	11 (1.1%)	0/11	0/11
	inhabitants	814	4 (0.5%)	1 (0.1%)	5 (0.6%)	0/5	0/5
	total	1,842	10 (0.5%)	6 (0.3%)	16 (0.8%)	0/16	0/16
Ōhama-chō	school children	2,232	16 (0.7%)	12 (0.5%)	28 (1.3%)	6/28 (21.4%)	4/28 (14.3%)
	inhabitants	4,423	142 (3.2%)	21 (0.5%)	163 (3.7%)	60/163(36.8%)	13/163(8.0%)
	total	6,655	158 (2.4%)	33 (0.5%)	191 (2.9%)	66/191(34.6%)	17/191(8.9%)

Table 2. Examinations of the Eriocheir japonicus

Name of river	Size of shell(mm) width X length	Sex	Gills left 1	2	3	4	5	6	right 1	2	3	4	5	6
Ōi-river	43 X 36	M	0	0	0	0	0	0	0	0	0	0	0	0
	48 X 42	M	0	0	0	0	0	0	0	0	0	0	0	0
	51 X 45	M	0	0	0	0	0	0	0	0	0	0	0	0
	54 X 50	M	0	0	0	0	0	0	0	0	0	0	0	0
	58 X 53	M	0	0	0	0	0	0	0	0	0	0	0	0
	63 X 55	M	0	0	0	0	0	0	0	0	0	0	0	0
	38 X 32	F	0	0	0	0	0	0	0	0	0	0	0	0
	41 X 34	F	0	0	0	0	0	0	0	0	0	0	0	0
Kiku-river	42 X 38	M	0	0	0	0	0	0	0	0	0	0	0	0
	43 X 38	M	0	1	0	0	1	0	0	0	1	0	0	0
	51 X 48	M	0	0	0	1	0	0	0	0	0	1	0	0
	52 X 46	M	0	0	0	0	0	0	0	0	0	0	0	0
	56 X 52	M	0	0	0	0	0	0	0	0	0	0	1	0
	60 X 55	M	0	0	0	0	0	0	0	0	0	0	0	0
	62 X 58	M	0	0	0	0	0	0	0	0	0	0	0	0
	64 X 60	M	0	0	0	0	0	0	0	0	0	0	0	0
	68 X 63	M	0	0	0	0	0	0	0	0	0	0	0	0
	45 X 40	F	0	0	0	0	0	0	0	1	0	0	0	0
	53 X 48	F	0	0	0	0	0	0	0	0	0	0	0	0
	54 X 50	F	0	0	0	0	0	0	0	0	0	0	0	0
	57 X 55	F	0	0	0	0	0	0	0	0	0	0	0	
	60 X 56	F	0	0	0	0	0	0	0	0	0	0	0	

Table 3. Results of intradermal test, complement fixation test and stool examination in Ohama-cho. (except the school children)

Name of sections	Number examined	Intradermal test (+)	(+)	Total	C.F.test (+)	Eggs (+)
KIKUHAMA	144	11 (7.6%)	0	11 (7.6%)	6/11	1/11
KUNIKANE	172	25 (14.5%)	1 (0.6%)	26 (15.1%)	12/26	7/26
KUNIYASU	364	24 (6.6%)	4 (1.1%)	28 (7.7%)	13/28	4/28
SEIBU	549	16 (2.9%)	2 (0.4%)	18 (3.3%)	6/18	0/18
TŌBU	490	11 (2.2%)	2 (0.4%)	13 (2.7%)	5/13	0/13
SAKASATO	147	2 (1.4%)	1 (0.7%)	3 (2.0%)	2/ 3	0/ 3
KAITO	104	9 (8.7%)	2 (1.9%)	11 (10.6%)	1/11	0/11
SHINKAWA	361	11 (3.0%)	1 (0.3%)	12 (3.3%)	1/12	0/12
NAKAGAWARA	205	3 (1.5%)	0	3 (1.5%)	1/ 3	1/ 3
TERABE	205	2 (1.0%)	2 (1.0%)	4 (2.0%)	0/ 4	0/ 4
ŌTA	158	5 (3.2%)	0	5 (3.2%)	1/ 5	0/ 5
MINAMI-ŌSAKA	196	1 (0.5%)	1 (0.5%)	2 (1.0%)	0/ 2	0/ 2
HŌCHI	336	5 (1.5%)	1 (0.3%)	6 (1.8%)	2/ 6	0/ 6
HAMANO-DAIICHI	319	7 (2.2%)	0	7 (2.2%)	0/ 7	0/ 7
HAMANO-DAINI	84	0	0	0		
HAMANO-SHINDEN	49	1 (2.0%)	1 (2.0%)	2 (4.1%)	0/ 2	0/ 2
HAMAKAWA	256	5 (2.0%)	1 (0.4%)	6 (2.3%)	4/ 6	0/ 6
MITSUMATA	284	4 (1.4%)	2 (0.7%)	6 (2.1%)	6/ 6	0/ 6
Total	4,423	142 (3.2%)	21 (0.5%)	163 (3.5%)	60/163	13/163

Fig. 2. Results of interdermal test in each sections in Ōhama-chō.

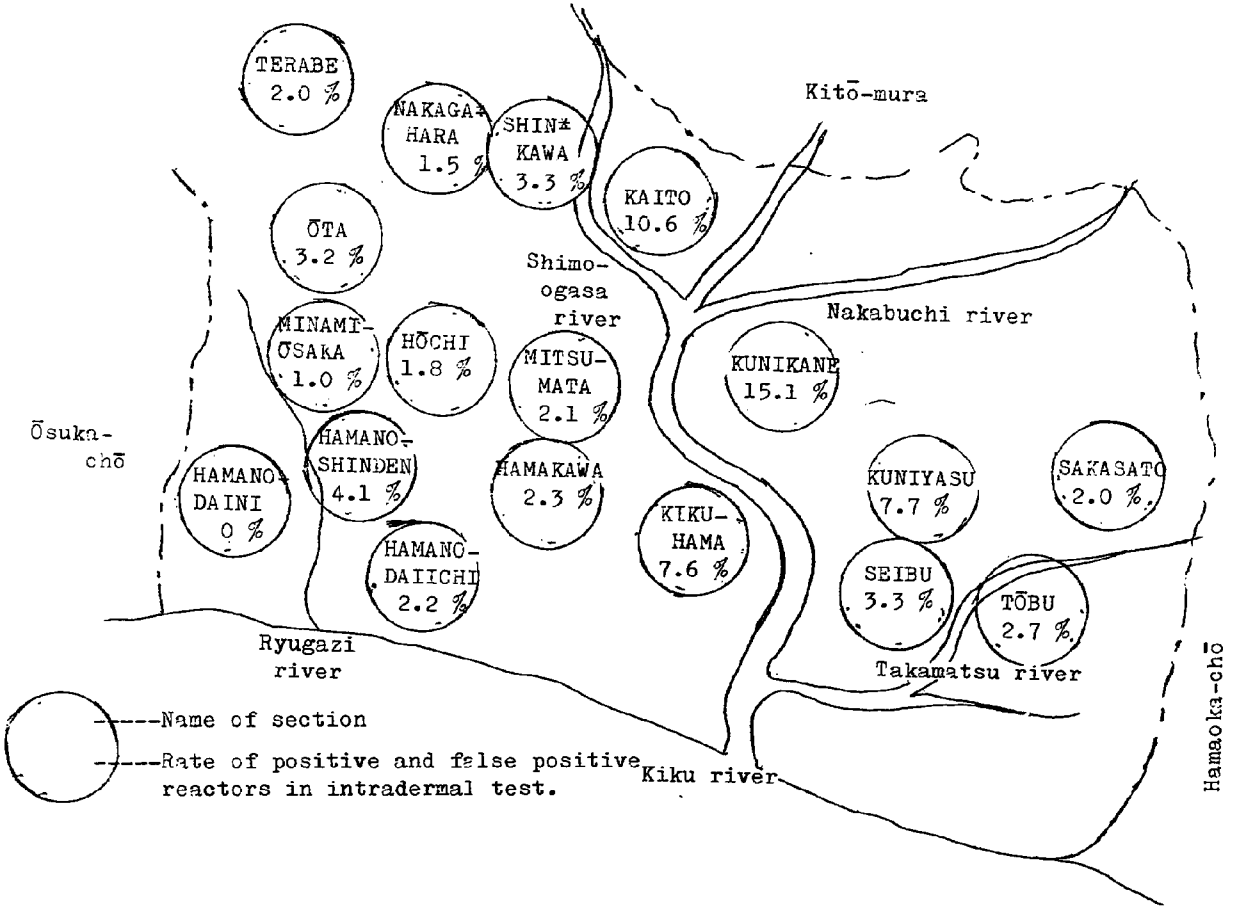
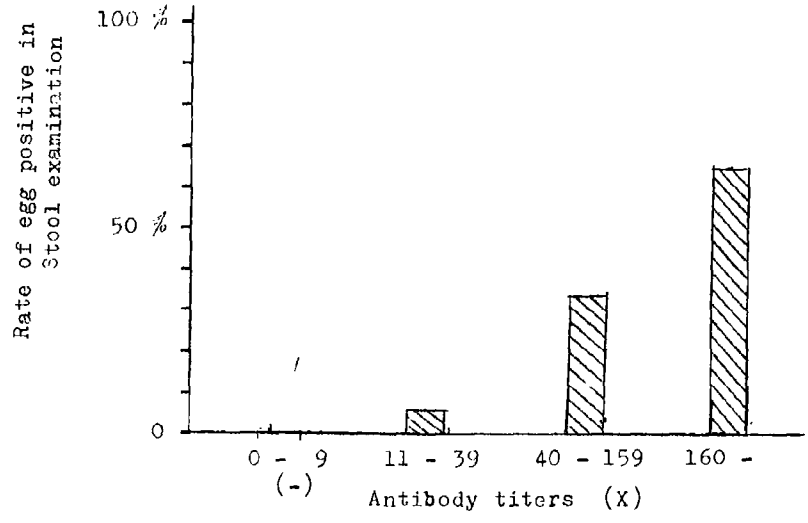


Table 4. Correlations among dilution titer of Antiserum in Complement-fixation test, Intradermal test and Stool examination.

titer of antibody \ intradermal test	Oigawa-Cho (+)	Oigawa-Cho (±)	Oigawa-Cho total	Ohama-Cho (+)	Ohama-Cho (±)	Ohama-Cho total
0 - X 9 (negative)	10 (0)	6 (0)	16 (0)	99 (0)	26 (0)	125 (0)
X 10 - X 39				32 (2)	7 (0)	39 (2)
X 40 - X159				9 (3)		9 (3)
more than X160				18 (12)		18(12)
total	10 (0)	6 (0)	16 (0)	158 (17)	33 (0)	191(17)

( ) : Number of egg positive persons in Stool examination.

Fig. 3. Relations between dilution titer of Antiserum in Complement-fexation test and rates of egg positive in stool examination.



C. Chemotherapy of Paragonimiasis with Bithionol.

IV. Clinical observations for 6 months after mass treatment in Ohama-oho, Shizuoka Prefecture.

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Introduction

The authors (Yokogawa, M., et al. 1961) reported in the previous paper III that 13 cases of paragonimiasis were treated with Bithionol (Bitin, Tanabe Co. Ltd., Japan) for the first time, and in all the cases the eggs of Paragonimus westermani both in the stools and in the sputa were disappeared by several administrations of this drug for a short period, and no relapses were seen from the follow-up observations for one year, and that the side-effects of this drug were confined to such transient and mild ones as diarrhea, tendency of loose passage, abdominal pain, nausea, vomiting or urticarial eruption and there was nothing detestable as medicinal toxicosis to be found. Based on the above mentioned results of the treatment, authors attempted this time the mass treatment for 16 cases of Paragonimiasis patients as the out-patients in the prevalent district of Ohama-cho in the western part of Shizuoka prefecture. The authors report the results of this treatment in the present paper.

Object and Method

Objects.

16 cases were selected as objects of the mass treatment, which were found by the screening method by means of intradermal test and complement fixation test among the inhabitants of this area and were proved to be Paragonimiasis patients by detection of paragonimus eggs in sputum or in stool.

These 16 cases as shown in Table 1. were 11 males and 5 females ranging from 12 to 66 years of age, and the supposed lapse of time from the onset of the disease to this treatment varied from 3 months to 9 years. And except 7 cases,* that is, those 4 cases which were found for the first time at the mass paragonimiasis examination conducted before the treatment and those 3 cases which were proved to have this disease from the beginning because of their symptoms of bloody sputa, 9 cases (56.2%) had been given chemotherapy of the pulmonary tuberculosis for the period from 6 months to 3 years with a wrong diagnosis, and 6 cases among them had continued their chemotherapy as the patients of the pulmonary tuberculosis up until the time when they were proved to be paragonimiasis by the authors. In all cases were noted the facts that they had eaten Eriocheir japonicus.

Method of therapy.

The daily dose of Bithionol** was determined to be 2.0g (30mg/kg-

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* Note: 5 cases among these 7 cases were given 20 to 50 ampullae of Emetine with the purpose of paragonimiasis treatment, but ended with no effect.

** Bitin, Tanabe Seiyaku Co. Ltd. Japan, was used.

50mg/kg) equally for all cases and given in 2 divided "takes" immediately after breakfast and dinner every other day. The number of times of the administration was 10, counting the daily dose of 2.0g for one. The patients were made to attend hospital every other day when they were to bring about 10g of stools for 2 days (the day and the day before) in the stool boxes handed beforehand, and asked for the side-effects, and then handed Bithionol for next two days.
Bithionol was administered separately at their homes. Besides in the case of the present mass treatment, no cases were prescribed rest and conducted the treatments under ordinary lives.

Methods of examination

(1) Stool examination.

For 2 days before the treatment and every day during the period of the administration of Bithionol, the number of eggs in 1gr. for stool (E. P. G., Eggs per gram) was counted by centrifugation technique using AMS III method. The same method was applied to observe the Paragonimus eggs in stool for 3 consecutive days every month after the completion of the treatment.

(2) Sputa examination.

The whole daily output of sputa were collected in sputum container, after examining whether it was bloody or not, it was dissolved with 2% NaOH (3 to 5 times as much as sputa and centrifugated to make egg counts.)

(3) Blood examination.

Before the treatment, immediately after the completion of the treatment, and every month after the treatment, erythrocyte counts, leukocyte counts, Hemoglobin determination, hemogram and erythrocyte sedimentation rate were observed and qualitative or quantitative changes of Blood were investigated.

(4) Intradermal test.

In order to investigate whether there could be found any difference in reactions to the intradermal test by V.B.S.* antigen and ppt** antigen before and after the treatment, the intradermal test by both

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* Veronal Buffered Saline extract prepared from the adults of P. westermani. (X10.000 dilution)

** Polypeptide extract prepared from the adults of P. westermani. (5γ/cc)

antigens were conducted before the treatment, immediately after the completion of the treatment and every month after the treatment and the increases of the diameters of the wheals caused by the intracutaneous injection of antigens were compared respectively. The intradermal test was carried out by injecting V.B.S. and ppt antigens intracutaneously on the volar surface of the left arm sufficient to raise the 3-4mm of the diameter of the wheal. And the length and the width of the ensuing wheals were respectively measured immediately and 15 minutes after the injection. The difference between the average value of the raised wheals immediately after injection and that of after 15 minutes was called the "increase of the diameter," and "the increase of the diameter " of the wheals are 5mm or more, 4mm, and 3mm or less were considered as positive, false positive and negative reactions respectively.

(5) Complement fixation test.

The complement fixation test was conducted with the sera taken before the treatment, immediately after the completion of the treatment and monthly after the treatment with the technique of the 50 percent end point titration of complement using V.B.S. antigen (X 5,000), and the changes of the antibody-titers were consecutively observed.

(6) The measuring of Bithionol in blood.

The authors asked this measurement to the laboratory of the Tanabe Seiyaku Co., Ltd. The blood concentration of Bithionol was measured about the serum taken during the period from 8th to 10th administration of Bithionol and from the immediately after the completion of the treatment to the 5th day after that.

(7) Chest-X-Ray examination.

Abnormal shadows seen in Chest-X-Ray before the treatment were classified and the change in each shadow was observed consecutively.

The Results of treatment and examinations

(1) The results of stool examination.

As mentioned above, all the individuals were given 2.0g daily dose of Bithionol for 10 times every other day, and the Paragonimus eggs in stools were all disappeared by the administrations from 2 times to 5 times and no recurrance has been found from the follow-up studies for 6 months from the completion of the treatment until present as shown in Table 2 and 3. And the maximum number of the Paragonimus eggs in 1gr. of stool counted by centrifugation technique using AMS III method (E.P.G.) was 867.

(2) The results of sputa examination.

The Paragonimus eggs were found during the period of the treatment in all 4 cases in which sputa could be examined, but all those eggs disappeared by the administration of this drug from 2 times to 4 times and no recurrence has been noted until now. And yet as the administration went on, sputum decreased both in quantity and frequency, and sputa, including bloody sputa, can not be found in all thease cases now. The maximum number of eggs found in the whole output of daily sputa were 231.

(3) Subjective Symptoms.

Bloody sputa: Bloody sputa were observed in 9 cases (56.2%) out of 16 cases as the subjective symptoms from the investigations on the case history. But bloody sputa were observed only in 4 cases during the treatment and disappeared by the administlation of this drung from 2 times to 4 times. After the treatment, no relapses has been observed until present, and almost all the cases showed disappearence not only of bloody sputa but of sputa.

Side-effects: As shown in Table 4., during the period of administration with Bithionol, 14 cases (87.5%) showed such side-effects as diarrhea and the tendency of loose stool, and vomiting (2 cases) and nausea (1 case) but no urticarial eruption was observed. Besides these symptoms were, like those in the previous hospitalized cases, all transient and mild and there was no necessity to stop the administration.

(4) The results of blood examination.

There were no remarkable changes in quality among the examinations on erythrocyte counts, leukocyte counts, and Hemoglobin determination, before and after the treatment as shown in Table 5; no qualitative or quantitative changes in leukocytes such as the appearance of immature cells shift to the left or decrease of lymph cells. The rate of eosinophiles before the treatment showed maximum 9%, but no remarkable effects were found after the treatment. Some of the cases which were recognized the quickning of the erythrocyte sedimentation rate before the treatment, improved after the treatment. However, most patients of these 16 cases, both the rate of eosinophiles and the erythrocyte sedimentation rate befor the treatment were found normal.

(5) The results of intradermal test.

No remarkable increase of the diameters of wheals in intradermal tests both with V.B.S. and ppt antigens was noted before and after the treatment as shown in Table 6 and 7; therefore according to the results of 5 months' observations, there were no reaction disappeared nor tendency

of reduction. Besides, as seen in 2 cases of the control, in spite of repeating of injections on almost the same site there has not been so far found any effect by sensitization with antigen at all.

(6) The results of complement fixation test.

The antibody titers in complement fixation test, gradually decreased from the time immediately after the treatment, and 14 cases wich could be observed consecutively (11 cases of them showed more than 1 : 160 dilutions serum before the treatment) all turned negative as shown in Table 8 and Fig 1; 1 case 1 month after the completion of the treatment, 1 case 2 months, 1 case 3 months, 5 cases 4 months, 5 cases 5 months respectively.

(7) Blood concentration of Bithionol.

As the blood concentration, 120 -180 γ of Bithionol in 1 ml. of serum were examined in the day of administrations from 8th to 10th dose, and 80 -150 γ in the next day of pause; and the blood concentration decreased gradually until the 5th day when Bithionol disappeared from the blood as shown in Fig. 2.

(8) The results of Chest-X-Ray examinations.

The authors examined before the treatment and have been observing from the time immediately after the treatment, and will report in the next paper.

Discussion

The authors proved Bithionol to be a very effective therapeuic drug of paragonimiasis and many other investigators are now being carried out further investigations. The results of them were all satisfactory in the efficacy of treatment. Besides, the side-effects, though there were some differences among dose and method of the administration or individuals, were such transient one as diarrhea, tendency of loose passage, abdominal pain, nausea, vomiting and urticarial eruption found during the period of the administration with this drug, and there were no such dangerous symptoms as chronic toxiosis, nor need to stop the administration owing to the side-effects. As all of the authors' and many other observers' cases so far have been hospitalized and given the treatment, the authors thought it necessary to investigate the similar effects could be expected in the case of nonhospitalized cases. And this time the authors attempted the mass treatment for the first time for 16 non-hospitalized paragonimiasis patients. And, as mentioned above, in the present mass treatment, the patients were not particularly put to rest cure but allowed to lead ordinary daily life; and accidentally

the treatments were conducted during the busy agricultural period and inspite of such circumstances as the patients were given treatment while being engaged in agricultural works, the efficacy and side-effects were not so much different from the previous hospitalized cases. The authors will compare the results of the treatment in the present non-hospitalized cases with those of the previous hospitalized cases in the following.

The efficacy of treatment and side-effects.

As for the disappearence of Paragonimus eggs, in the present non-hospitalized cases, they disappeared with the administrations from 2 to 5 doses in stools with 2 to 4 doses in sputum, while on the previous hospitalized group were with the administration from 2 to 5 doses both in stools and in sputum; there could not be seen any differences between those two groups treated with Bithionol.

As for bloody sputa, they disappeared with the administrations from 2 to 4 doses in non-hospitalized cases, while the hospitalized cases were with the administrations of from 1 to 6 doses in the cases of the hospitalized; there could hardly be found a difference. Besides no recurrence both in Paragonimus eggs and in bloody sputa has been found from the follow-up studies for 6 months.

As to the side-effects caused by the administration of Bithionol, they were mainly symptoms on digestive organs such as diarrhea, tendency of loose passage, nausea or vomiting, which were all transient and mild, and it was not necessaly to stop the administration due to the side-effects. These facts which observed in the non-hospitalized cases were quite the same as in the hospitalized cases. From the results above mentioned, it could be proved that the non-hospitalized treatment achieved safely and had therapeutic effects satisfactory.

Intradermal test.

It was often said that, once infected with this disease, the intradermal test with V.B.S. antigen keeps positive reaction for such a long period as 10 to 20 years even after the cure of the disease, while the test by ppt antigen often shows negative reaction when negative for eggs. The authors thereby investigated consecutively the changes in the intradermal test after turning negative for the Paragonimus eggs by the treatment. However, from the results of the follow-up studies for 6 months, the tendency to reduced the diameters of the wheals with both of antigens were not found. Besides the authors observed the effects of the intradermal test to the partial immunity of sensitization of the skin site by the repeated inoculations of antigens but found no effects at all in either group of treatment or of the control. And the authors intend to keep further observation hereafter.

Complement fixation test.

Yokogawa (1956, 1961) has often described that the close relations were found between the complement fixation test in paragonimiasis and the survival of worms, and reported in the previous paper that this test could serve quite effectively as a method of investigation to decide the cure of this disease. That is, in the previous 11 cases of hospitalized treatment, the tendency of reduction of antibody titers were found immediatly after the completion of the treatment, and all the cases became negative within one year. In the present non-hospitalized group of treatment, too, the antibody titers of 14 cases which could be observed consecutively turned negative within 6 months: 1 case in the first month, 1 case in the second month, 1 case in the third month, 5 cases in the fourth, 6 cases in the fifth month. Again those hospitalized cases whose antibody titers were examined under X 50 and above X 160 before the treatment, turned negative within 5 months and during the period from 6 months to 12 months respectively, thereby it seemed that the lower the antibody titer before treatment, the earlier it turned negative. In the present hospitalized cases, too, 11 cases out of 14 cases showed the antibody titers above X 160 before the treatment, turned negative during the period from 3 to 5 months, 1 case of X 27 turned negative in the 1 month and 1 case of X 63 in the 2 month after the completion of the treatment, thus showing the tendency that the lower the antibody titer, the earlier it turned negative just as before, but as for the time of turning negative, some differences were noted between 2 groups of treatment. On this point, the authors hope to keep further investigation hereafter.

Blood Concentration of Bithionol.

The authors (Yokogawa et al, 1961) reported that 3 healthy adults were given 50mg/kg of Bithionol every other day and measured the blood concentration, and the result was that after the initial dose the blood concentration of Bithionol in 1 ml. sera reached 121γ-154γ during the time from 27 hours to 75 hours in the day of administration, and decreased down to 83γ-97γ in the day of pause. This time the authors observed the blood concentration before and after the completion of the administration (that is, from the day of 8th administration to the 5th day after the completion of the administration and the dily dose 40γ-50γ mg/kg, every other day), and the result was 120γ-180γ in the day of administration and 80γ-150γ in the day of pause, and Bithionol in the blood disappeared on the 5th day after the completion of 10th administrations. From the results of this measuring, the authors could not find any remarkable difference of blood concentration between the former and the latter period of treatment. Accordingly, there may be no cumulative phenomenon by consecutive administration and proved that about 80γ-180γ of Bithionol were continually kept in blood through the period of the treatment.

Of course, the method of measuring the blood concentration of

Bithionol may not be complete and the broken down form of this drug can be mixed in the blood, and so the above mentioned rates of measurement cannot soon be taken as the concentration rate which concerns with the killing of worms. According to the report by Miyagawa et al. (1955), it is said that the maximum rate of the blood concentration of Emetine when injected 10mg/kg was 10γ/cc, and it decreased down to under 2γ/cc in the 12 hours after the injection, and at the same time the combined use of Sulfonamids is considered to serve for the purpose of keeping the blood concentration. In the case of Bithionol, the concentration of such high rate was kept continually in the living body and there was no cumulation phenomenon noted; this is thought to be one of the reasons why this drug is excellent as a drug for remedy.

The above mentioned results were got from the follow-up studies for 6 months after the completion of the treatment and authors have kept now further observations consecutively. The satisfactory processes are found just as the previous group of the treatment and all the cases are thought to be cleared completely judging from the results of stool examinations and complement fixation test. The fact that non-hospitalized treatment was carried out safely and surely, which was especially the purpose of the present attempt, may serve a great deal for the future aspect of the treatment of paragonimiasis.

Summary

Bithionol was given to 16 paragonimiasis patients as the non-hospitalized mass treatment for the first time and the following results were noted by the 6 months' observation.

1) The same efficacy of treatment as in the hospitalized treatment was found in the case of non-hospitalized mass treatment. No relapses nor increase of side-effects could be found.
2) Intradermal test showed neither disappearance nor tendency of reduction after the treatment, and there could not be found any effects of sensitization of the skin site caused by the repeated injection of antigen.
3) As for complement fixation, it was noted that lower the antibody titer before the treatment earlier it turned negative, and even the cases whose antibody titers were above X 160, all turned negative within 5 month after the completion of the treatment.
4) The blood concentration of Bithionol found no remarkable difference between the former and the latter period of the treatment 80γ/cc-180γ/cc of Bithionol were kept in blood continually all through the period of the treatments, and disappeared on the 5th day after the completion of the administrations.

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Table 1. Description of 16 cases treated with Bithionol.

Case No.	Name	Age	Sex	Lapse of time from the onset of disease to the treatment	Subjective symptome	Past history with respect to treatment
1	H. Y.	12	M	3 months	-	-
2	A. H.	14	F	3 years	Pleuritis (3 years ago)	SM PAS INAH
3	H. K.	14	M	1 year	blood phlegm	SM PAS INAH
4	M. H.	14	F	1 year	blood phlegm	SM PAS INAH
5	A. K.	42	M	6 years	blood phlegm	Emetine
6	A. H.	18	M	2 years	-	SM PAS INAH
7	A. I.	32	M	3 months	-	-
8	A. H.	59	M	4 years	blood phlegm	SM PAS INAH Emetine
9	H. C.	62	F	6 months	blood phlegm	SM PAS INAH
10	A. K.	16	M	4 years	blood phlegm	SM PAS INAH Emetine
11	A. T.	49	F	3 months	-	-
12	M. N.	38	F	2 years	-	SM PAS INAH
13	M. K.	66	M	3 months	-	-
14	Y. S.	31	M	9 years	blood phlegm	Emetine
15	S. H.	20	M	3 years	blood phlegm	SM PAS INAH Emetine
16	K. I.	59	M	4 months	blood phlegm	-

Remarks : SM Streptomycine
PAS Para-amino-salicylic acid
INAH Iso-nicotinic acid hydrazide

Table 2. Results of treatment with Bithionol

Case No.	Name	Age	Sex		Before treatment 1	Before treatment 2days	During treatment (Days and times of administration of Bithio 1 1	2	3 2	4	5 3	6	7 4	8	9 5	10	11 6	12	13 7	14	15 8	16	17 9
1	F.Y.	12	M	a.	54	73	11	113	5	12	6	1	2	0	4	0	0	0	0	0	0	0	0
				b.			S		S		S		S		S		S						S
2	A.S.	14	F	a.	7	3		2		4	1		0	0	0	0	0	0	0	0	0	0	0
				b.							S				S	S		S	S		3		
3	F.K.	14	M	a.	5	4	8		0	0	1	2	1	0		0		0	0	0	0	0	0
				b.			V S						S					S					
4	M.H.	14	F	a.	21	26	11	3	3	2	4	0	0	0	0	0	0	0	0	0	0		0
				b.			V S	S	S														
5	A.K.	42	M	a.	162	72	33	11	14	18	12		1	1	0	0	0	0	0	0	0	0	0
				b.			S	S	S						S								
				c.	(+)			(+)		(+)	-	-	-										
6	A.H.	18	M	a.	377	509		401	204	201	26	20	0	1	0	0	0	0	0		0	0	0
				b.																			
7	A.I.	32	M	a.	12	4	8	28	3	0	3	2	1	0	0	0	0	0	0	0	0	0	0
				b.					S	S	S	S	S		S		S	S			S		S
8	A.H.	59	M	a.	18	8	5	0	7	5	4	0	4	0	0	0	0	0	0	0	0	0	0
				b.			S	S	S		S		S	S	S	S	S		S		S		S
9	H.C.	62	F	a.	5	12	24	2	3	5	2	3	1		0	0	0	0	0	0	0		0
				b.			D		S	S	S	S	S	D	S	S	S		S	S	S		S
10	A.K.	16	M	a.	428	867	624	280	849	96	148	6	14	6	5	2	0	0	0	0	0	0	0
				b.			S	S	S						S						S		
11	A.T.	44	F	a.	18	32	26	6	10	4	2	1	0	0	0	0	0	0	0	0	0	0	0
				b.			S	S	S	S	S		S		S		S		S		S		S
12	M.M.	38	F	a.	31	58	18	28	9	3	1	4	1	1	0	0	0	0	0	0	0	0	0
				b.			N S	S	S	S	S		S		S	S	S		S		S		S
13	M.K.	66	M	a.	0	0	3	0	0	4	2	4	0	0	0	0	0	0	0	0	0	0	0
				b.			S	S	S	S	S		S	S	S		S		S		S	S	S
14	Y.S.	31	M	a.	2	0	7	2	0	4	0	2	0	0	0	0	0	0	0	0	0	0	0
				b.																			
				c.	(+)	(+)			(+)	(+)													
15	S.H.	20	M	a.	0	0	0	0	3	0	4	0	0	0	0	0	0	0	0	0	0	0	0
				b.			S		S	S					S								
				c.		(+)		(+)			(+)		-	(+)	-		-	-					-
16	K.I.	59	M	a.	3	3	6		0		1	1	0	0	0	0	0	0	0	0	0	0	0
				b.									S						S	S			S
				c.	(+)	(+)		(+)			(-)				-								

Remarks : a. Number of paragonimus eggs in stool (E.P.G.)
b. Side effects D :Diarrhea. S :Soft stools. V :Vomiting. N :Naus
c. Eggs in sputa (+):Sputa are bloody and positive for paragonimus egg
(-):Sputa are bloody and negative for paragonimus egg
- :Sputa are not bloody and negative for paragonimus

1

2. Results of treatment with Bithionol

During treatment (Days and times of administration of Bithionol)																			After treatment						
2	3 2	4	5 3	6	7 4	8	9 5	10	11 6	12	13 7	14	15 8	16	17 9	18	19 10times	20days	1	2	3	4	5	6	months
13	5 S	12	6 S	1	2 S	0	4 S	0	0 S	0	0	0	0	0	0 S	0	0	0	0		0	0	0	0	
2		4	1 S		0	0	0 S	0 S	0	0 S	0 S	0	0 S	0	0	0	0 S	0	0		0	0	0	0	
	0	0	1	2	1 S	0		0		0 S	0	0	0	0	0	0	0	0		0	0	0	0	0	
3 S	3 S	2	4	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0		0	0	0	
.1 S +)	14 S	18 (+)	12 -	-	1 -	1	0 S	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	
)1	204	201	26	20	0	1	0	0	0	0	0		0	0	0	0	0	0	0	0				0	
'8	3 S	0 S	3 S	2 S	1 S	0	0 S	0	0 S	0 S	0	0	0 S	0	0 S	0	0	0	0	0	0	0	0	0	
0 S	7 S	5	4 S	0	4 S	0 S	0 S	0 S	0 S	0	0 S	0	0 S	0	0 S	0	0 S	0	0	0	0	0	0	0	
2	3 S	5 S	2 S	3 S	1 S	D	0 S	0 S	0 S	0	0 S	0 S	0 S		0 S	0	0 S	0	0	0	0	0	0	0	
0 S	849 S	96	148	6	14	6	5 S	2	0	0	0	0	0 S	0	0	0	0	0	0	0	0	0	0	0	
6 S	10 S	4 S	2 S	1	0 S	0	0 S	0	0 S	0	0 S	0	0 S	0	0 S	0	0 S	0	0	0	0	0	0	0	
8 S	9 S	3 S	1 S	4	1 S	1	0 S	0 S	0 S	0	0 S	0	0 S	0	0 S	0	0 S	0	0	0	0	0	0	0	
0 S	0 S	4 S	2 S	4	0 S	0 S	0 S	0	0 S	0	0 S	0	0 S	0 S	0 S	0	0 S	0	0	0	0	0	0	0	
2	0	4	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	(+)	(+)																							
0	3 S	0 S	4	0	0	0	0 S	0	0	0	0	0	0	0	0	0	0	0		0				0	
+)			(+)		-	(+)	-		-	-					-		-								
	0		1	1	0 S	0	0	0	0	0	0 S	0 S	0	0	0 S	0	0	0	0	0	0	0	0	0	
+)			(-)				-																		

of paragonimus eggs in stool (E.P.G.)

fects D :Diarrhea. S :Soft stools. V :Vomiting. N :Nausea.

sputa (+):Sputa are bloody and positive for paragonimus eggs.
(-):Sputa are bloody and negative for paragonimus eggs.
- :Sputa are not bloody and negative for paragonimus eggs.

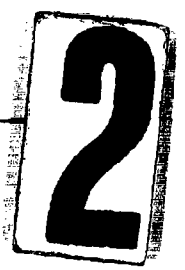


Table 3. Variations in E. P. G. in stools and the clearance after the administration of Bithionol. (Sedimentation techniques with the A. M. S. III method)

Days	Cumulative number of the doses	No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
			M	F	M	F	M	M	M	M	F	M	F	F	M	M	M	M
(Before treatment)		1	54	7	5	21	162	377	12	18	5	428	18	31	0	2	0	3
		2	73	3	4	26	72	509	4	8	12	867	32	58	0	0	0	3
1	1		11		8	11	33		8	5	24	624	26	18	3	7	3	6
2			113	2		3	11	401	28	0	2	280	6	28	0	2	0	
3	2		5		0	3	14	204	3	7	3	849	10	9	0	0	4	0
4			12	4	0	2	18	201	0	5	5	96	4	3	4	4	0	
5	3		6	1	1	4	12	26	3	4	2	148	2	1	2	0	0	1
6			1		2	0		20	2	0	3	6	1	4	4	2	0	1
7	4		2	0	1	0	1	0	1	4	1	14	0	1	0	0	0	0
8			0	0	0	0	1	1	0	0		6	0	1	0	0	0	0
9	5		4	0		0	0	0	0	0	0	5	0	0	0	0	0	0
10			0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
11	6		0	0		0	0	0	0	0	0	0	0	0	0	0	0	0
12			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 4. Subjective symptoms of the paragonimiasis patients Before, During and After treatment with Bithionol.

	Case No.	blood phlegm	diarrea or soft stocls	nausea	vomiting	abdominal pain	urti-carial eruption
Before treatment	1						
	2						
	3	+					
	4	+					
	5	+					
	6						
	7						
	8	+					
	9	+					
	10	+					
	11						
	12						
	13						
	14	+					
	15	+					
	16	+					
during treatment	1		+				
	2		+				
	3		+		+		
	4		+		+		
	5		+				
	6						
	7		+				
	8		+				
	9		+				
	10		+				
	11		+				
	12		+	+			
	13		+				
	14						
	15		+				
	16		+				
after treatment	1						
	2						
	3						
	4						
	5						
	6						
	7						
	8						
	9						
	10						
	11						
	12						
	13						
	14						
	15						
	16						

Table 5. Results of the Blood examination.

Case No. Sex		red cells ($X10^4$)	white cells	hemo-globin (%)	B	E	N 1	N 2	N 3	N 4	L	Mon	E.S.R.
1 M	a.	466	7,400	75	0	5	2	18	21	12	36	6	15
	b.	491	7,600	74	0	7	3	12	24	13	33	8	11
	c.	477	6,600	79	0	4	4	13	27	11	33	8	
2 F	a.	409	7,200	95	0	6	2	19	24	7	38	4	15
	b.	480	7,700	94	0	4	0	13	21	11	40	6	18
	c.	452	7,400	94	0	5	2	11	23	8	36	4	12
3 M	a.	485	6,000	86	0	3	1	16	25	16	29	10	4
	b.	531	6,800	85	0	6	3	11	24	12	38	6	1
	c.	490	6,400	84	0	6	1	8	29	14	37	5	2
4 F	a.	516	7,800	87	0	2	2	16	28	12	42	8	20
	b.	485	7,800	84	0	4	3	14	21	6	43	9	28
	c.	467	6,800	89	0	4	0	15	23	15	35	8	16
5 M	a.	493	8,000	92	0	3	0	16	26	8	38	9	43
	b.	417	7,300	94	0	6	3	12	21	11	41	6	49
	c.	455	6,400	98	0	3	3	13	26	15	32	8	16
6 M	a.	428	9,000	86	0	6	1	18	28	12	29	6	9
	b.	393	8,400	90	0	4	0	15	20	10	46	5	9
	c.	464	7,800	93	0	5	2	13	24	9	36	11	11
7 M	a.	494	7,600	90	0	4	2	13	20	15	37	9	5
	b.	499	7,200	88	0	7	0	16	25	7	37	8	5
	c.	500	7,600	85	0	5	4	13	21	16	35	6	9
8 M	a.	420	7,100	95	0	4	1	17	26	12	32	7	3
	b.	430	6,800	89	0	3	4	14	24	16	33	6	1
	c.	410	6,400	100	0	3	2	11	26	15	32	9	3
9 F	a.	430	6,900	95	0	4	3	9	21	13	46	4	23
	b.	386	6,200	90	0	6	1	13	26	18	31	5	22
	c.	464	7,600	95	0	4	1	15	26	9	36	8	11
10 M	a.	436	8,600	85	0	6	2	10	26	11	41	4	45
	b.	412	8,000	83	0	6	3	14	26	16	37	8	18
	c.	530	7,000	100	0	4	1	9	28	13	37	8	15
11 F	a.	354	6,800	85	0	8	0	18	24	9	38	3	21
	b.	410	6,600	72	0	6	1	13	28	13	31	8	10
	c.	387	5,200	80	0	9	0	16	23	15	33	4	14
12 F	a.	389	7,400	75	0	6	2	12	24	14	37	5	17
	b.	409	6,800	70	0	2	0	18	21	11	40	8	17
	c.	430	6,800	82	0	4	1	13	23	15	39	4	13

M	c.	490	6,400	84	0	6	1	8	29	14	37	5	2
4 F	a.	516	7,800	87	0	2	2	16	28	12	42	8	20
	b.	485	7,800	84	0	4	3	14	21	6	43	9	28
	c.	467	6,800	89	0	4	0	15	23	15	35	8	16
5 M	a.	493	8,000	92	0	3	0	16	26	8	38	9	43
	b.	417	7,300	94	0	6	3	12	21	11	41	6	49
	c.	455	6,400	98	0	3	3	13	26	15	32	8	16
6 M	a.	428	9,000	86	0	6	1	18	28	12	29	6	9
	b.	393	8,400	90	0	4	0	15	20	10	46	5	9
	c.	464	7,800	93	0	5	2	13	24	9	36	11	11
7 M	a.	494	7,600	90	0	4	2	13	20	15	37	9	5
	b.	499	7,200	88	0	7	0	16	25	7	37	8	5
	c.	500	7,600	85	0	5	4	13	21	16	35	6	9
8 M	a.	420	7,100	95	0	4	1	17	26	12	32	7	3
	b.	430	6,800	89	0	3	4	14	24	16	33	6	1
	c.	410	6,400	100	0	3	2	11	26	15	32	9	3
9 F	a.	430	6,900	95	0	4	3	9	21	13	46	4	23
	b.	386	6,200	90	0	6	1	13	26	18	31	5	22
	c.	464	7,600	95	0	4	1	15	26	9	36	8	11
10 M	a.	436	8,600	85	0	6	2	10	26	11	41	4	45
	b.	412	8,000	83	0	6	3	14	26	16	37	8	18
	c.	530	7,000	100	0	4	1	9	28	13	37	8	15
11 F	a.	354	6,800	85	0	8	0	18	24	9	38	3	21
	b.	410	6,600	72	0	6	1	13	28	13	31	8	10
	c.	387	5,200	80	0	9	0	16	23	15	33	4	14
12 F	a.	389	7,400	75	0	6	2	12	24	14	37	5	17
	b.	409	6,800	70	0	2	0	18	21	11	40	8	17
	c.	430	6,800	82	0	4	1	13	23	15	39	4	13
13 M	a.	421	6,100	85	0	4	1	16	24	9	42	4	19
	b.	454	7,600	80	0	5	0	17	21	13	35	6	20
	c.	459	7,600	87	0	8	0	9	25	13	40	5	14
14 M	a.	492	6,300	90	0	5	1	9	26	12	40	7	2
	b.	481	6,100	94	0	3	0	12	21	16	43	5	4
	c.	520	6,000	114	0	6	0	13	24	10	38	9	1
15 M	a.	488	8,800	95	0	6	1	11	26	12	39	5	5
	b.	477	8,400	97	0	5	0	16	21	18	32	8	5
	c.	453	8,100	100	0	8	2	5	29	11	42	3	3
16 M	a.	418	6,800	80	0	4	1	18	23	13	38	3	19
	b.	394	8,300	75	0	8	1	11	21	11	43	7	23
	c.	421	6,600	78	0	6	1	16	24	12	33	8	11

a.--- before treatment
b.--- immediately after 10 times medication
c.--- 3 months after treatment

Table 6. Changes of the increase of diameters of wheal with V. B. S. antigen on the individuals before, during and after treatment with Bithionol. (unit : m m)

Case No.	Age	Sex	Before treatment	During treatment 5th day	10th day	After treatment 1 month	2	3	4	5	6	Average
1	12	M	4	5	4	7	-	5	5	6	-	5.1
2	14	F	13	11	10	8	-	8	13	9	-	10.3
3	14	M	14	10	8	-	10	9	9	9	10	9.9
4	14	F	11	11	10	7	7	10	7	7	8	8.7
5	42	M	14	8	12	12	15	22	-	15	9	13.7
6	18	M	8	14	8	8	-	-	-	-	-	9.5
7	32	M	8	7	8	7	10	8	9	8	8	8.1
8	59	M	18	9	11	13	7	14	16	16	7	12.3
9	62	F	17	18	16	8	17	10	16	-	-	14.6
10	16	M	17	18	5	5	8	6	9	8	-	9.5
11	49	F	8	6	8	11	8	10	16	7	9	9.2
12	38	F	13	10	8	8	6	9	7	-	8	8.6
13	66	M	6	5	9	8	8	8	7	-	-	7.3
14	31	M	12	15	17	10	22	14	18	13	-	15.1
15	20	M	11	8	8	-	15	-	-	-	-	10.5
16	59	M	11	10	9	8	18	8	11	10	9	10.4
Average			11.6	10.3	9.4	8.6	11.6	10.1	11.0	9.8	8.5	10.1
(Control)												
1	9	M	3	3	1	1	1	0	0	0	0	1.0
2	13	M	1	3	0	0	0	1	0	0	0	0.6
Average			2.0	3.0	0.5	0.5	0.5	0.5	0	0	0	0.8

Table 7. Changes of the increase of diameters of wheal with ppt antigen on the individuals before, during and after treatment with Bithionol. (unit : m m)

Case No.	Age	Sex	Before treatment	During treatment 5th day	During treatment 10th day	After treatment 1	2	3 (month)	4	5	6	Average
1	12	M	3	4	4	5	-	3	2	2	-	3.3
2	14	F	8	8	7	5	-	11	6	9	-	7.7
3	14	M	10	5	6	-	7	9	5	9	6	7.1
4	14	F	8	10	7	7	10	6	7	6	5	7.3
5	42	M	8	6	7	10	9	11	-	14	9	9.3
6	18	M	5	8	6	5	-	-	-	-	-	6.0
7	32	M	6	5	7	8	8	7	9	7	5	8.0
8	59	M	13	17	9	9	7	12	10	13	10	11.1
9	62	F	10	17	9	9	9	8	12	-	-	10.6
10	16	M	6	6	5	5	4	5	7	6	-	5.5
11	49	F	8	6	7	9	6	9	7	10	6	7.6
12	38	F	7	4	5	6	6	8	5	-	6	5.9
13	66	M	3	3	4	4	6	2	2	-	-	3.4
14	31	M	10	7	10	11	7	8	7	12	-	9.0
15	20	M	8	6	7	-	6	-	-	-	-	6.8
16	59	M	8	8	9	15	10	7	14	8	6	9.4
Average			7.6	7.5	6.8	7.7	7.3	7.6	7.2	7.8	6.8	7.4
(Control)												
1	9	M	0	0	0	0	2	0	0	0	0	0.2
2	13	M	0	0	0	0	0	0	1	0	0	0.1
Average			0	0	0	0	1	0	0.5	0	0	0.2

Table 8. Changes of dilution titer of Antiserum in Complement-fixation tests on the individuals before, during and after treatment with Bithionol.

Case No.	Age	Sex	Before treatment	After 10 times medication	1 M.	2 M.	3 M.	4 M.	5 M.	6 M.
1	12	M	X 63	X 49	X 20	-	-	-	-	
2	14	F	> X160	> X160	X150		X 33	X 10	-	
3	14	M	> X160	> X160		X 64	X 41	X 11	-	-
4	14	F	> X160	X 93	X 29	X 13	-	-	-	-
5	42	M	> X160	> X160	> X160	X 40	X 42		-	-
6	18	M	> X160	> X160	> X160					
7	32	M	> X160	> X160	X108	X 40	X 22	-	-	-
8	59	M	> X160	> X160	X148	X 94	X 93	X 11	-	-
9	62	F	> X160	> X160	> X160	>X160	X 29	-		
10	16	M	> X160	> X160	> X160	>X160	X 57	X 12	-	
11	44	F	> X160	> X160	X 51	X 25	X 14	-	-	-
12	38	F	> X160	X106	X 40	X 26	X 11	-		-
13	66	M	X 27	X 11	-	-	-	-		
14	31	M	> X160	> X160	X 50	X 54	X 40	X 11	-	
15	20	M	> X160	> X160		X 95				
16	59	M	> X160	> X160	X108	X 43	X 24	-	-	-

Fig. 1. Changes of dilution titer of Antiserum in Complement-fixation tests on the individuals treated with Bithionol.

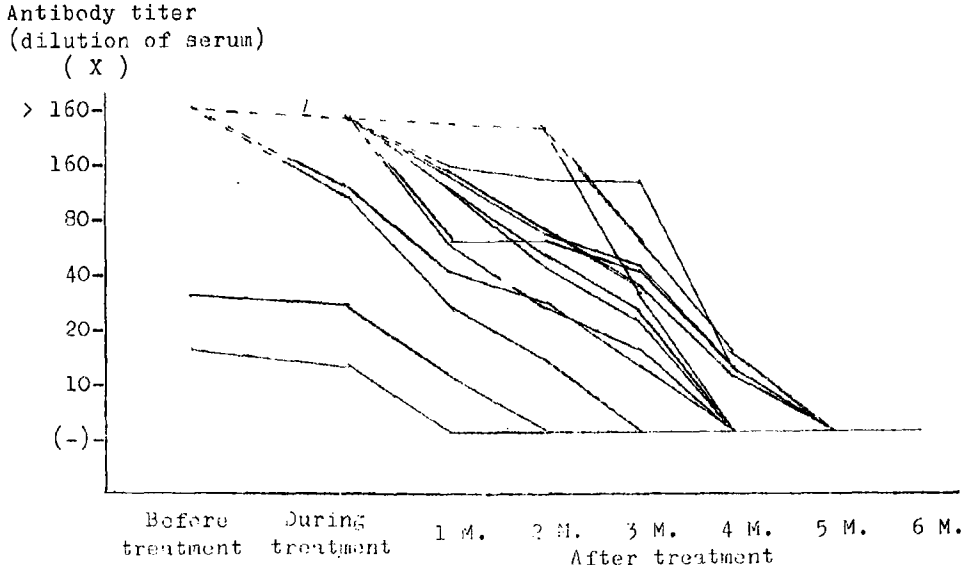
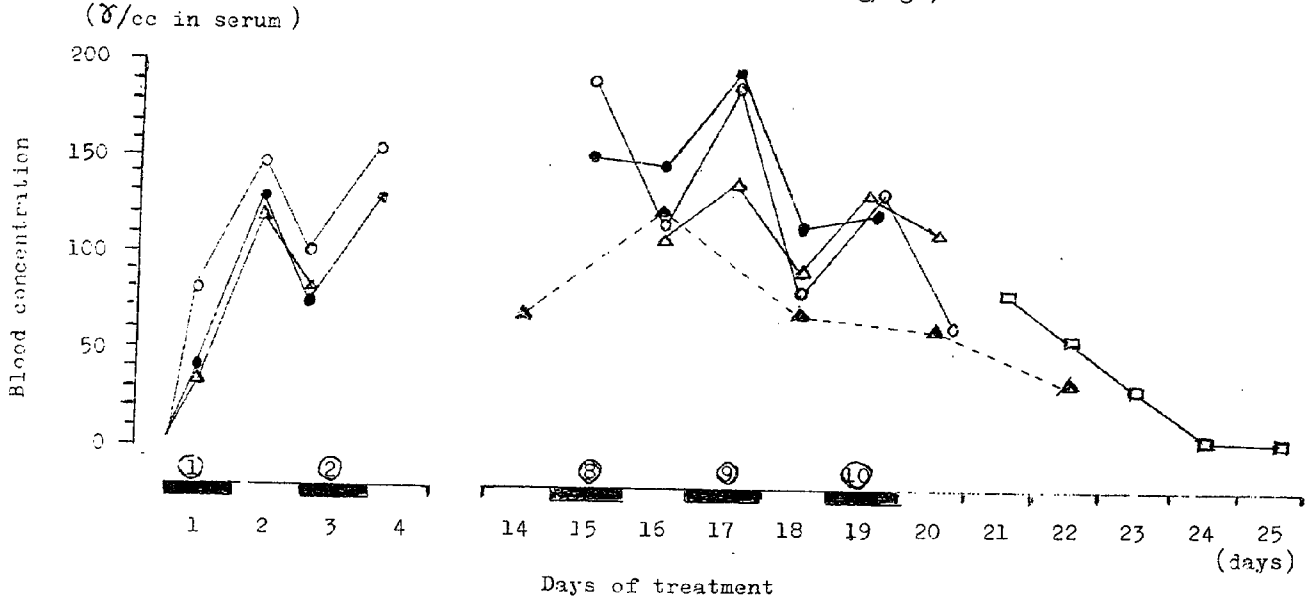


Fig. 2 Blood concentration of Bithionol

(Dose administrated 35-50mg/kg)



D. Studies on the Complement fixation test for Paragonimiasis as the method of criterion of cure.

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Introduction

It is well recognized that paragonimiasis is one of the most important tropical disease in Asia, especially in Japan, Korea, China and Formosa. But the accurate treatments for this disease were not found until quite recently.

Recently, Yokogawa et al. (1960) found that Bithionol is quite effective for this disease and several other investigators have been confirmed the efficacy of this drug. However, there are many questions to decide the recovery of paragonimiasis after treatment by sputum and stool examinations for ova. For example, the parasites sometimes may show on interruption of the ovulation only during the period of treatment and may begin the ovulation soon after treatment so it is oftenavery difficult to decide the cure of this disease during short period after treatment. Yokogawa (1953) reported that the examination for ova in sputam and stool shuld be followed up at least for more than 3 months after the treatment to decide the cure of paragonimiasis and also Yokogawa (1961) reported that positive reaction in complement fixation test for paragonimiasis would turn negative soon after the complete recovery of this dicease. In this study, the authors conducted to use the complement fixation test for evaluation of the effect of treatment for paragonimiasis. The complement fixation tests were followed up before, during and after treatment on 48 paragonimiasis patients treated with the combined method with emetine hydrochloride and sulfonamide or Bithionol. So it is often very difficult to decide the cure of this disease during short period after treatment. Yokogawa (1953) reported that the examination for ova in sputum and stool shuld be followed up at least for more than 3 months after the treatment to decide the cure of paragonimiasis. And also Yokogawa (1961) reported that positive reaction in complement fixation test for paragonimiasis would turn negative soon after the complete recovery of disease. In this study the authors conducted to use the complement fixation tests for evaluation of the effect of treatment for paragonimiasis.

Object and Method

The sera for the complement fixation test were prepared periodically from the paragonimiasis patients bef re, during and after the treatment with Bithionol or the combined method of emetine hydrochloride and sulfonamid, and the changes of antibody titers in complement fixation test were compared with the technique of the 50 percent and point titration of complement. (Yokogawa et al, 1956).

Namely, 1:5,000 of V.B.S. antigen prepared from adults of Paragonimus westermani as the same method of V.B.S. antigen for skin test was employed in this test and 2.5 50 percent hemolysis units of complement were used. More than 1:10 in dilution of the serum at the 50 percent hemolysis end point titration was considered as the positive reaction

in this test. The details of this test was described in the previous report (Yokogawa et al., 1956, 1961), so ommited to described in this paper.

The sera of the patients for complement fixation test were inactivated as soon as possible after sero-separations and kept in -20°C. These sera were tested at the same time under the same conditions. From the results of our detailed studies, it was proved that no significant differences were found in the antibody titers of complement fixation test carried out with those sera which were stored in -20°C and those which were used immediately after sero-separated.

Results

The results of Complement-fixation tests carried out periodically on 48 human cases of paragonimiasis summarized in Table 1, 2 and 3. 25 cases out of 48 cases were treated with emetine combined with sulfonamid, and the rests of them were treated with Bithionol.

These 48 cases were divided into 3 groups as follows.

Group 1: 11 cases, which were treated with emetine combined with sulfonamid for 12 days and were seemed to be completely cured.

Group 2: 12 cases, which were treated with emetine combined with sulfonamid as same as group 1, but were ineffective.

Group 3: 25 cases, which were given 5-15 doses of Bithionol every other day and cured completely.

On group 1, the paragonimus eggs in stools and sputa disappeared completely during the period from 10th days to 40th days and no ova were found during the follow-up studies for 8 months after treatment. The antibody titers in complement fixation test in all these patients decreased gradually with lapse of time after the treatment and became negative as shown in Table 1 and Fig. 1.

On group 2, the therapeutic effects were not recognized at all in spite of the same treatments were given same as group 1. As shown in Table 2, in 5 cases paragonimus eggs in stools and sputa were not cleared during the period of the treatment and in 7 cases the eggs were cleared for a chile but the eggs were found again during the period from 2 months to 4 months after the treatment. The antibody titers of them in complement fixation test showed only strong fluctuation and no tendency decrease.

On group 3, the paragonimus eggs in stools and sputa were cleared during the period from the 4th days to 6th days after the beginning of the treatment and no relapses were found during the period from 6 months to 12 months after the treatment. The antibody titers in complement fixation tests showed the tendency of decrease as group 1 and became negative during the period from 1 month to 12 months after the treatment.

From the above mentioned results, the variations of antibody titers in complement fixation tests were summarized as follows. The antibody titers of all the cases in group 1 and 3 which had cured completely

showed a tendency of decrease soon after the treatment and finally became negative. On the contrary, on the cases in group 2 which were ineffective, the antibody titers showed only a strong fluctuation but a negative reaction. Accordingly, it may be possible to guess the therapeutic effects in early stage after the treatment through the periodical observations of complement fixation tests. No relations were found among the antibody titers, age, sex and lapse time of infection of the patients.

Discussion

The Complement fixation tests for paragonimiasis has been introducted by Ando (1910), and he pointed out from the results of animal experiments that it is helpful to evaluate the efficacies of treatments for paragonimiasis. Recently, Yokogawa et al (1956) reported the method and the diagnostic value of complement fixation test in human paragonimiasis. Yokogawa (1956,1961) has also often described that the complement fixation test for paragonimiasis is closely connected with the survival of the worm, Paragonimus westermani in the final hosts. That is, the intradermal test using V.B.S. antigen keeps positive reactions during the long period from 10 years to 20 years after the recovery of paragonimiasis. On the contrary, the antibody titers in complement fixation test became negative after the death of the worm in the final hosts. Accordingly, the complement fixation test would be helpful to evaluate the effects of treatment. Yokogawa (1956) reported that the antibody titers of the patients who received lobectomy to remove the worm cyst in the lung decreased gradually and became negative within the period of 6 months after operations.

Kushi et al (1960) and Takano (1960) recognized the same results as Yokogawa from the results of follow up studies on paragonimiasis patients who had cured completely with treatment of emetine combined sulfonamid, and reported that the complement fixation test is one of the suitable methods to decide the cure of paragonimiasis after treatment.

Takano (1960) carried out the rapid flocculation tests with bentonite antigen and cholesterol lecithin antigen on the patients treated with various drugs, and reported that the tendency of decrease of antibody titers in the tests were recognized when the drugs were effective.

However, the results of rapid flocculation test seemed to be instable and its method is quite complicated compared with those of complement fixation test.

Conclusion

The changes of the antibody titers in complement fixation tests were studied periodically on 48 paragonimiasis patients before, during and after treatment. The antibody titers of the patients who had cured with the treatments of emetine-sulfonamid or Bithionol showed a tendency of decrease immediatly after treatment and finally became negative during

the period from 5 months to 12 months after the treatment. On the contrary, the antibody titers of the patients who were not cured showed only a strong floctuations but negative reaction.

It was confirmed that it may be possible to evaluate the efficacies of the treatments from the results of complement fixation tests in the early stage after treatment.

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11) Yokogawa, M., et al. (1956): On the complement fixation test for Paragonimiasis. Relation between the intradermal test and the complement fixation test. Nihon Izi Shimpo, 1703, 27-35. (in japanese)

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Table 1. Changes of dilution titer of Antiserum in Complement-fixation tests on the individuals before and after treatment with Emetine hydrochloride combined with Sulfonamid. (effective cases --- Group No. 1)

Case No.	Before treatment	After treatment 1 M.	2 M.	3 M.	4 M.	5 M.	6 M.	7 M.	8 M.
1	> X160	> X160	X 54		X 39			X 16	-
2	> X160	X 89	X 14			-	-		
3	> X160	X 80	X 10			-			
4	> X160	X 54	X 23	X 17		X 11		-	
5	> X160	X 40	X 32			X 31			-
6	> X160	X 40			X 10	-			
7	X149	> X160		X 28		X 12			-
8	X145	X123		X 33		X 25	X 25		-
9	X120	X 62		X 24		-			
10	X 20	X 25		X 10		-			
11	X 16	X 33		X 15		X 16	-		

Fig. 1. Changes of dilution titer of Antiserum in Complement-fixation tests on the individuals before and after treatment with Emetine hydrochloride combined with Sulfonamid. (effective cases --- Group No. 1)

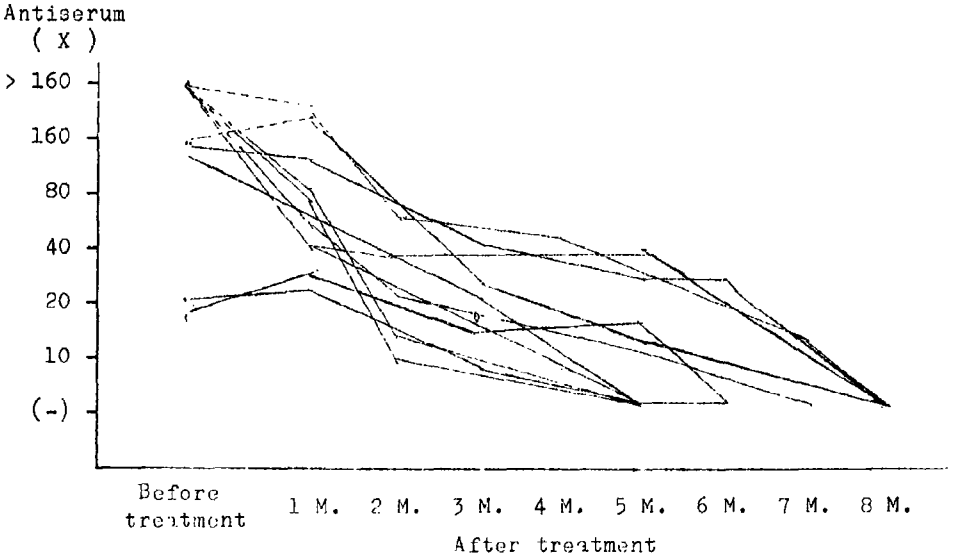


Table 2. Changes of dilution titer of Antiserum in Complement-fixation tests on the individuals before and after treatment with Emetine hydrochloride combined with Sulfonamid. (Ineffective cases --- Group No. 2)

Case No.	Before treatment	After treatment 1 M.	2 M.	3 M.	4 M.	5 M.	6 M.	Notes
1	> X160	> X160	> X160	> X160	> X160			ineffectiveness
2	> X160	X117	X150	X160	> X160			relapsed
3	> X160	X 62	X 81	X 96				ineffectiveness
4	> X160	X 40	X 33	X 76	X 20	X 32		relapse
5	X 93	X 46	X 20	X 28	X 34			relapse
6	X 85	X144	X104	X133				ineffectiveness
7	X 84	X 75	X 74	X 67	X 58	X 40		relapse
8	X 65	X 17	X 40	X 23				ineffectivemess
9	X 53	X 20	X 70	X 67	X 28	X 26		relapse
10	X 38	X 54	X 30	X 32				ineffectiveness
11	X 23	X 45	X 27	X 18	X 16	X 19	X 12	relapse
12	X 20	X 32	X 23	X 85	X 65	X 17	X 12	relapse

Fig. 2. Changes of dilution titer of Antiserum in Complement-fixation tests on the individuals before and after treatment with Emetine hydrochloride combined with Sulfonamid. (ineffective cases --- Group No. 2)

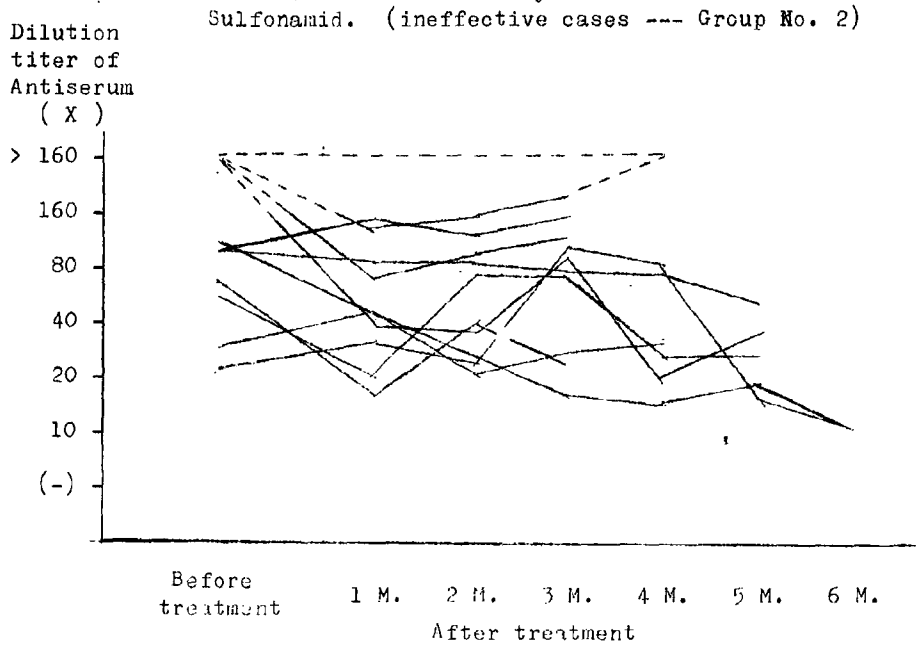
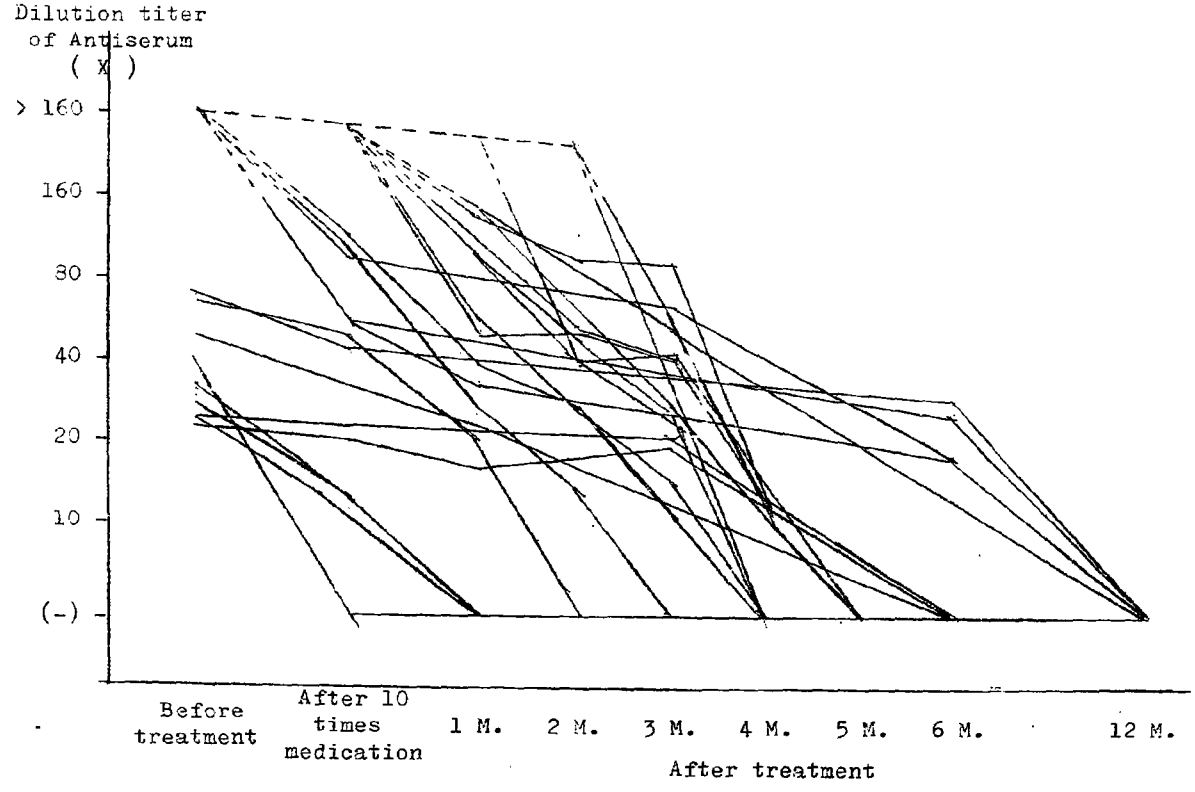


Table 3. Changes of dilution titer of Antiserum in Complement-fixation tests on the individuals before and after treatment with Bithionol (effective cases --- Group No. 3)

Case No.	Before Treatment	After 10 times medication	After treatment 1 M.	2 M.	3 M.	4 M.	5 M.	6 M.	12 M.
1	> X160	> X160	> X160	> X160	X 57	X 12	-		
2	> X160	> X160	> X160	> X160	X 29	-			
3	> X160	> X160	> X160	X 40	X 42		-	-	
4	> X160	> X160	X150		X 33	X 10	-		
5	> X160	> X160	X148	X 94	X 93	X 11	-	-	
6	> X160	> X160			X 45				-
7	> X160	> X160		X 64	X 41	X 11	-	-	
8	> X160	> X160	X108	X 43	X 24	-	-	-	
9	> X160	> X160	X108	X 40	X 22	-	-	-	
10	> X160	> X160	X 50	X 54	X 40	X 11	-		
11	> X160	> X160	X 51	X 25	X 14	-	-	-	
12	> X160	X106	X 40	X 26	X 11	-		-	
13	> X160	X 93	X 29	X 13	-	-	-	-	
14	> X160	X 87			X 55			X 18	-
15	> X160	X 53	X 32					X 18	-
16	> X160	X 53						X 24	-
17	X 68	X 41						X 28	-
18	X 63	X 49	X 20	-	-	-	-		
19	X 47		X 22					-	-
20	X 40	-	-					-	
21	X 31	X 12	-					-	
22	X 29	X 12	-					-	
23	X 27	X 11	-	-	-	-			
24	X 25	X 23			X 20			-	-
25	X 22	X 20	X 15		X 19			-	-

Fig. 3. Changes of dilution titer of Antiserum in Complement-fixation tests on the individuals before and after treatment with Bithionol (effective cases --- Group No. 3)



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In the present studies the following facts were obtained:
(1) Bithionol has specific effect in paragonimiasis and is not toxic from the follow-up studies for one year after treatment with Bithionol.
(2) This drug can be also effectively used for mass-treatment of paragonimiasis patients as out-patients.
(3) Criterion of cure of paragonimiasis judging by the disappearance of ova from the excreta is not always easy. The more exacting the criteria of cure, the longer the patients are followed up. However, serial examinations of the complement-fixation test after treatment is valuable for the criterion of cure.

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(4) The new endemic area of paragonimiasis was found in west district of Shizuoka prefecture by using intradermal test, complement-fixation test and stool examinations.

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